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Reinhard ANGELMAR
Pierre A. MORGON
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Reinhard Angelmar*

Pierre A. Morgon**

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* The Salmon and Rameau Fellow of Healthcare Management, Emeritus, Emeritus Professor of Marketing at INSEAD, Boulevard de Constance 77305 Fontainebleau Cedex, France.
Email: reinhard.angelmar@insead.edu

** Vice President, Franchise & Global Marketing Strategy, Sanofi Pasteur, Lyon, France.

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Abstract

This chapter focuses on the marketing of preventive (prophylactic) vaccines. Preventive vaccines differ from therapeutic pharmaceuticals in a number of ways and pose distinctive marketing challenges. We first provide background information on the vaccine industry. We next analyze the main players carrying out the consumer, buyer and payer roles, and then move to a discussion of the key vaccine marketing decisions. We then summarize important trends, and conclude with a discussion of promising research questions.

1 Background on vaccines

Vaccines are biological pharmaceuticals. Like other biologicals such as insulin, the active components of vaccines are extracted from living organisms and then isolated through separation technologies. What differentiates vaccines from other biologicals is their distinctive mechanism of action: they work by stimulating or restoring the immune system's ability to fight infections and disease.

Until recently, all vaccines were preventive or prophylactic vaccines¹, that is, they were developed to prevent a future infection or attenuate its effects. In April 2010, the FDA approved Provenge, the first therapeutic vaccine, for use in male patients with metastatic prostate cancer.² Other therapeutic vaccines are under development, including vaccines against other types of cancers and Alzheimer's (Shirvill, 2010; Andrews, 2011). Figure 1 shows how vaccines are related to other types of pharmaceuticals.

Therapeutic vaccines, besides representing only a very small share of vaccine sales at this time, pose pricing and reimbursement issues (Provenge costs \$93,000 for a course of treatment) and marketing challenges which are similar to those of other therapeutic biologics³. Preventive vaccines, however, face distinctive marketing challenges and a somewhat different market environment.

Consumers are motivated to seek therapeutic treatment because they experience a current health problem, whereas preventive vaccination requires that consumers anticipate a future health problem. Marketers of preventive vaccines therefore must ensure consumer awareness of the risks of infectious disease and motivate them to take preventive action. This is particularly challenging when past vaccination campaigns have virtually eradicated a vaccine target. Beneficial outcomes from therapeutics are often easily observable because of the resulting improvement in health status (e.g., pain reduction), whereas a successful preventive vaccination does not improve the health status of the vaccinated person and can even sometimes deteriorate it due to adverse events. To perceive the benefits of prevention, individuals must engage in counterfactual thinking (Roese, 1997), e.g., "If I had not gotten the flu shot, I would have caught the flu". While receiving less credit for benefits than therapeutics, preventive vaccines are easily blamed when previously healthy persons experience health problems which may be unrelated to the vaccination. Stories of healthy people presumably made sick by vaccines are very attractive for the media and may lead to an exaggerated perception of the risks of vaccination and skepticism about its value among the lay public.

Ensuring an accurate perception of the benefit – risk balance therefore represents another distinctive challenge for marketers of preventive vaccines.

Many therapeutics are for chronic disease and involve daily or weekly use. Consumers therefore have an opportunity to learn from direct experience and develop intimacy with their treatment, which influences their decision to continue or switch. Except for seasonal flu vaccines, the vast majority of preventive vaccines are administered only once or very infrequently during a life time (e.g., every ten years for tetanus booster shots). Personal use experience, therefore, plays no or a very small role in preventive vaccine treatment decisions, which are based on other sources of information such as health care professionals, advertisements, friends, information on the internet, and other media (Kennedy, Basket & Sheedy, 2011; Freed, Clark, Butchart et al., 2011; Maurer et al., 2010).

Both therapeutics and preventive vaccines have a direct effect on the health of treated individuals. Preventive vaccines in addition have an indirect “herd-protective” effect by reducing inter-individual transmission and thereby lowering the risk of infection among unvaccinated persons (Smith, P.G., 2010). For example, it is estimated that a 50% HPV vaccination rate of women will result in a 47% reduction in cervical cancer incidence, with 1 in 4 cases prevented among non vaccinated women (Bogaards et al., 2011). When individuals do not take these positive externalities into account, market failure may result, namely less vaccination than is efficient from a societal point of view (Fine & Clarkson, 1986). The possibility of market failure provides a rationale for governmental interventions such as subsidies to consumers and mandatory vaccination. Mandatory vaccination, which is controversial because it restricts individual freedom in the interest of collective benefits, is another differentiating feature of preventive vaccine public markets.

Governments and supranational organizations play an even more central role in the preventive vaccine market than for therapeutics. They often subsidize R&D and manufacturing investments in vaccines, may own vaccine manufacturers⁴, are important buyers and payers of vaccines, issue vaccination recommendations, and mandate vaccinations. Moreover, governments and supranational organizations may take responsibility for the distribution, administration and marketing of preventive vaccines through public health campaigns.

Because of their distinctive characteristics compared to therapeutics, this chapter focuses on preventive vaccines.

2 The vaccine industry

Based on companies' annual reports, global 2010 sales of the leading vaccine manufacturers are estimated at \$23.1 billion (Andrews, 2011). Assuming that these companies account for 80% of the total market (Kresse and Shah, 2010), this values the global vaccine market at \$28.8 billion, or 3.4% of the total 2010 global pharmaceutical sales of \$856 billion (IMS Health, 2011).

Like for all pharmaceuticals, vaccine sales are generated mainly in high-income countries. For 2008, it was estimated that 77% of global vaccine sales came from high-income markets comprising 14% of the world's population and 8% of the world's birth cohort (Morgon, 2011). The U.S. represents the largest sales region (34.6% of 2009 global vaccine sales), followed by the European Union (30.4%), Japan (7.9%), China (7.4%), and India (6.4%) (Sahoo, 2010).

2.1 Vaccine industry structure

The five largest vaccine manufacturers (GlaxoSmithKline, Sanofi, Merck & Co, Pfizer, Novartis) are also among the six largest pharmaceutical manufacturers overall, although not in the same order (see Table 1). They account for 80% of global vaccine sales, which is considerably higher than the 27% share of global pharmaceutical sales for the top five pharmaceutical companies. Except for Roche and Lilly, the top ten pharmaceutical companies have stepped up their investments in the vaccine sector in recent years, signaling the growing strategic role of vaccines in their corporate portfolio.

At 29% (GlaxoSmithKline) and 32% (Sanofi Pasteur) the operating profit margins of the two leading vaccine companies are comparable to the average 30% margin of originator pharmaceutical companies (Table 2). The significantly higher costs of goods sold of vaccines (38% versus 21% of sales) are compensated mainly by lower marketing, sales and administrative costs (17% versus 31%). The higher vaccine costs of goods sold reflects the high capital intensity, the cost of highly qualified labor required by complex manufacturing processes, and the cost of meeting more stringent quality requirements. The lower marketing, sales & administrative expenses result from the greater buyer concentration due to the high share of vaccines purchased by governments, and the smaller number of prescribers, who are mostly pediatricians plus, for flu vaccines, GPs and respiratory specialists.

In addition to the big five, three other large pharmaceutical companies, namely AstraZeneca, Abbott, and Johnson & Johnson, have recently increased their presence in the vaccine sector (Kresse & Shah, 2010). Some 50 other manufacturers are located mostly in low-

and mid-income countries. They generated 20% of the global vaccine sales in value and 86% in volume (WHO, UNICEF, World Bank, 2009). Most of these are local players who supply their domestic markets with low-cost high-volume old-technology vaccines. In recent years, a number of firms especially from India have upgraded their quality, obtained WHO prequalification, and become suppliers to public markets in other low- and middle-income countries. As vaccine manufacturers in China raise their manufacturing quality levels to meet WHO standards⁵, competition in low- and middle-income countries as well as in supra-national tenders will further intensify, including competition for innovative vaccines. Some of the emerging market manufacturers have become suppliers of innovative products thanks to a combination of in-house R&D and strategic alliances, which have provided them with access to the required technologies (Milstien and Kaddar, 2010).

The big five vaccine manufacturers dominate the markets of North America, Latin America and Western Europe. Markets in most other regions are dominated by local manufacturers. For example, in 2009 local manufacturers captured 77% of the market in China, 42% in India and 68% in Russia (see Table 3). The Japanese vaccine market is also dominated by local manufacturers, with non-Japanese companies accounting for a mere 4% of vaccine sales (Andrews, 2011)⁶. To increase their position in countries where their presence is still low, the big five have engaged in a multitude of deals and alliances with local manufacturers (Kresse & Shah, 2010).

Concentration is very high in many franchises and indications. For example, Pasteur had a 100% share of the Meningitis vaccine market in North America in 2009 (see Figure 4). In the U.S., 57% of the 30 vaccine/age classes with ACIP-recommended vaccines had only one manufacturer, 33% had two, and only 9 classes had between 3 and 5 manufacturers in 2008 (see Table 4). In Western Europe, two companies accounted for 100% of the HPV vaccine market, and three companies for 94% of the pediatric vaccine market in 2008 (see Figure 5). Like for therapeutics, concentration is higher for novel types of vaccines than for older vaccines.

The high concentration in most high-income countries is the result of the exit of many manufacturers from the vaccine industry over the last forty years combined with a low entry rate. For example, the number of companies manufacturing vaccines in the U.S. declined from 26 in 1967 to 17 in 1980 and to 3 in 2004 (Berndt et al., 2009). Countries such as China which currently still have a large number of vaccine manufacturers, are likely to experience future industry consolidation. Low-quality manufacturers will leave the industry as regulatory

agencies raise quality standards, price competition fueled by overcapacities will reduce the number of flu vaccine manufacturers, and multinational companies will acquire emerging country players with low-cost high-volume manufacturing capabilities to compete in middle-income countries and multi-country public market tenders. Examples are Sanofi Pasteur's acquisition of the Indian company Shanta Biotechnics, and the acquisition of the Chinese company Tianyuan by Novartis.

2.2 Entry barriers

Entry barriers are high, especially for entry into classes with innovative vaccines, and in high-income countries.

Product patents play a lesser role in the vaccine industry compared to therapeutics, although they can play a role for specific antigens, adjuvants, manufacturing technologies (e.g., in hepatitis B vaccine production), and administration technologies (e.g., intra-dermal administration). Because of the complex production, clinical development and regulatory approval processes, know-how in these domains represents a significant barrier to entry.

Manufacturing scale-up typically occurs in late phase II, and decisions to build expensive manufacturing capacity to scale must be made years before regulatory approval. Unlike the multi-purpose manufacturing facilities for small-molecule pharmaceuticals, vaccine facilities for bulk antigen production are generally uniquely dedicated and therefore are sunk costs (Berndt et al., 2009).

High regulatory costs are another important barrier to entry. Clinical trials designed to show the efficacy of flu vaccines require large number of subjects because a low attack rate drives the need to power the clinical studies to demonstrate efficacy. Serious yet rare side effects detected for a vaccine raise the regulatory hurdles for similar vaccines. For example, subsequent to the market withdrawal of a previous rotavirus vaccine (RotaShield) due to rare but fatal adverse effects, Rotateq pre- and post licensure safety studies ended up enrolling 70,000 children.

High fixed manufacturing and regulatory costs result in substantial scale economies. The size of a vaccine market relative to the minimum efficient scale therefore is an important determinant of entry (Scherer, 2007; Danzon & Pereira, 2011), which explains why there are more competitors in the large flu vaccine market than in most other, much smaller markets (see Figure 4). Moreover, because vaccines are biological products, generics cannot use the low cost abbreviated new drug application (ANDA) process that has resulted in rapid and deep market penetration by generic versions of small-molecule therapeutics in many countries. The resulting

longer product life cycles of vaccines compared with small molecules are reflected in higher residual values in vaccine deal NPV calculations.

2.3 Threat of substitutes, and supplier power

Vaccines face two types of substitutes: alternative methods for preventing an infection, and therapies for dealing with the consequences of being infected. For example, forthcoming malaria vaccines will compete with alternative prevention methods such as mosquito nets, insect repellents and preventive drugs such as Lariam (mefloquine), as well as antimalarial medications such as artemisinin. Sexual abstinence to prevent HPV infection is one type of substitute for HPV vaccines, and therapies for genital warts, as well as pap testing and therapies for cervical cancer are other kinds of substitutes for HPV vaccines. Anti-virals such as Tamiflu and Relenza, which are administered to flu-stricken persons, are substitutes for flu vaccines. A price increase and/or performance decline of substitutes should increase the demand for vaccines and vice versa. Phelps (1978) and Nordquist and Wu (1976) have indeed shown that an increase in the price of curative medical care increases the demand for prevention, and demand for prevention may decline when health insurance lowers the price of curative care (Kenkel, 2000).

As far as suppliers are concerned, some markets for critical vaccine manufacturing technologies and equipments (e.g., ultra centrifuges) are dominated by one or two suppliers, who command significant bargaining power. Small biotech and technology providers with valuable and rare technologies are also in a strong bargaining position vis-à-vis vaccine manufacturers.

3 Vaccine customers

Like for therapeutics, the key customer roles of (1) consuming (receiving the vaccination), (2) buying (selecting the vaccine) and (2) paying (financing the purchase) are typically carried out by different persons or organizations. Table 5 provides examples of persons and organizations carrying out these roles in the vaccine market, and Figure 5 shows a customer map.

We first describe the two main types of customer role configurations, namely private and public markets, and then discuss the following stakeholders: consumers, vaccine prescribers, organizations issuing vaccination recommendations, vaccine purchasers, and vaccination advocates and opponents.

3.1 Private and public markets

Vaccine markets are characterized as “private” or “public” markets, depending on who the buyers and payers are. In private markets, consumers and/or private insurers are the buyers and payers, whereas public players such as federal and regional governments buy and pay in public markets. Each specific vaccine generally competes in both private and public markets, with the sales mix depending on the characteristics of the vaccine target group (e.g., age and risk status), the country or region, and the disease threat. In the U.S., purchases through public-sector programs account for slightly more than half of the market (in number of doses) for pediatric vaccines (for children 0 to 6 years of age), decline to one third for adolescent vaccines (7 to 18 years of age) (Shen, Rodewald & Birkhead, 2009), with public financing for adult vaccines lagging behind (Orenstein et al., 2007). When a vaccine is indicated for multiple age-groups, who pays often depends on the age of the vaccinated person. For example, public programs pay for HPV-vaccines for many adolescent women but not for adult women (KFF, 2011). The importance of private versus public buyers and payers also varies across countries and regions. In the Africa-Middle East – Eastern Europe region, the private / public shares are estimated at 26/74, compared to 55/45 for the Asia-Pacific region (Sanofi Pasteur, 2009). Public players generally dominate when there are pandemic disease threats, as was the case for the 2009/2010 H1N1 influenza. Decisions made by public customers influence decisions in the private market. For example, private insurers in the U.S. tend to cover vaccines recommended for public purchase.

3.2 Consumers

Global vaccination rates for some vaccines and sub-groups infants and children are high, e.g., 85% for DTP, 86% for polio, 85% for measles and 75% for hepatitis B. But vaccination rates vary greatly across regions, countries (WHO, 2011), and within countries. For example, the 2009 pandemic flu vaccination rate ranged between 4.8% and 92% across 12 countries and different population sub-groups (Brien et al., 2011). The 2010 U.S. national vaccination rate of children aged 19-35 months with pneumococcal conjugate vaccine was 83.3%, ranging from 70.8% in Nevada to 91.1% in Connecticut (Centers for Disease Control and Prevention, 2011). Similar disparities in vaccination rates exist for other types of vaccines.

3.2.1 The consumer vaccination decision process

Why do some people get vaccinated and others not? To get vaccinated, an individual must engage in a number of behaviors including (1) accessing the health care system, (2)

discussing vaccination with a health care professional, (3) deciding to get vaccinated, (4) complying with vaccination.

Health care system access. Whereas children in high-income countries typically undergo a series of routine visits with health care professionals such as pediatricians, many children in low income countries do not have access to the health care system. But even in high income countries not everybody receives health care. In the US, 10.5% of all children under 18 years had no health care visit to an office or clinic within the past 12 months, rising to 43% among uninsured children (National Center for Health Statistics, 2011).

Vaccination discussion. Every health care visit is an opportunity to discuss vaccination. But while most physicians routinely check immunization at wellness or health maintenance visits, far fewer discuss vaccination during illness or acute care visits, in which urgent concerns dominate (Schaffer et al., 2001; Szilagyi et al., 2005; Szilagyi et al., 2008; Humiston et al., 2008). And wellness visits are less frequent than illness visits, especially among adolescents, for whom only 9% of visits were for preventive care (Rand et al., 2007). The effectiveness of patient reminder and recall systems for improving vaccination rates in primary care is reviewed by Jacobson & Szilagyi (2005).

Vaccination decision. A vaccination discussion may or may not result in a decision to get vaccinated. Among adolescent girls (11-17 years) in the U.S., 26% were recommended to receive the HPV vaccine by their health care provider, but only 49% of them actually received the HPV vaccine (Palli et al., 2010).

Vaccination can be voluntary or mandatory. Mandatory vaccination may be imposed by legislation and private organizations. All 50 U.S. states require certain vaccinations for children entering public schools.⁷ State mandates also exist for entry to colleges and universities⁸, long-term facilities, health care workers⁹, and other groups. However, many jurisdictions allow exemptions from vaccination requirements for medical or religious reasons, or when parents have philosophical or personal belief objections to vaccination.¹⁰

Compliance. Compliance is an issue whenever two or more doses and corresponding visits are required for effective vaccination. A study in the context of the 3-dose HPV vaccination found that 72% of US female adolescents (11 to 21 years) would need to make 3 visits in addition to their habitual physician visits if the vaccine were initiated at a preventive visit (Rand et al., 2007). Another study among young women (18 to 24 years) recruited by a university health clinic who were offered the 3-doses HVP vaccine series for free found that

just over half (50.7%) received the first dose, 78.3% of whom returned to receive the second dose, and 55.7% of these returned for the third dose (Moore et al., 2010).

3.2.2 Determinants of consumers' vaccination behavior

Differences in consumers' vaccination behavior have been related to socio-demographic and social psychological variables.

Socio-demographic variables associated with vaccination include age, health status, gender, education, income, profession, race/ethnicity, and religion. For example, being aged 65 years and over or suffering from chronic illness or working in the medical field was the strongest predictor for having received the influenza vaccination across 11 European countries (Endrich et al., 2009). Increasing parental educational attainment was significantly associated with higher influenza vaccination uptake among U.S. college dormitory students (Uddin et al., 2010). Combined seasonal or H1N1 influenza vaccination coverage among the U.S. population aged ≥ 6 months was higher among non-Hispanic whites compared with non-Hispanic blacks and Hispanics (Setse et al., 2011). Religion was negatively associated with vaccination in the U.S. (Doyle et al., 2010a) and the Netherlands (Ruijs et al., 2011).

Many studies have investigated relationships between social psychological variables and vaccination intentions and behavior. The main conceptual frameworks underlying these studies are the health belief model (Becker, 1974; Rosenstock, 1974), Rogers' protection motivation theory (Rogers, 1975, 1983), the theory of reasoned action (Fishbein and Ajzen, 1975), and the theory of planned behavior (Ajzen, 1988, 1991). The key constructs of these frameworks tend to overlap and include the following: (1) the perceived threat from a disease, (2) the attitude toward vaccination, (3) norms, and (4) behavioral control / self-efficacy beliefs. Additional factors investigated include anticipated regret, and past vaccination behavior.

3.2.2.1 Perceived threat/risk from a disease

The perceived threat or risk from a disease (e.g., Brewer et al., 2004; Chapman & Coups, 2006; Weinstein et al., 2007) is a key construct in the health belief and protection motivation models. The perceived risk from influenza was significantly positively associated with medical students' vaccination intentions (Betsch & Wicker, in press). A low perceived risk of contracting pertussis was the main reason for not receiving tetanus diphtheria acellular pertussis (Tdap) vaccination (Miller et al., 2011). Perceived risk is based on the perceived likelihood of getting a disease (personal vulnerability/susceptibility), and the perceived

seriousness or severity of the disease. Both can vary greatly across different ethnic groups (Timmermans et al., 2005).

The perceived likelihood of getting a disease is influenced by its prevalence, which economists see as an important driver of the demand for prevention: the higher (lower) the prevalence, the higher (lower) the demand for prevention (Philipson, 2000). The prevalence-elasticity hypothesis predicts that the growth of infectious diseases is self-limiting because rising prevalence motivates preventive action such as vaccination, which reduces prevalence. It also predicts that vaccination success lays the ground for the return of an infectious disease because it reduces the future motivation to vaccinate. Prevalence-elasticity can explain why in many high-income countries childhood diseases which were virtually eradicated thanks to a very high pediatric vaccination rate, were followed by a decline in pediatric vaccination rates, which has led to a resurgence of childhood diseases. For example, measles is re-emerging in Europe, with 85% of the cases being unvaccinated.¹¹ In France, which accounts for more than half of the reported cases 2011, the upsurge is attributed to a decline in the vaccination rate (Benkimoun, 2011). Funk et al. (2010) review a number of models for explaining the dynamics of the disease prevalence – prevention behavior relationship.

Consumer beliefs about risk factors related to individual characteristics can also affect the perceived likelihood of getting a disease (personal vulnerability/susceptibility) and, therefore, the motivation for vaccination. For example, young women with a greater number of sexual partners had a high level of interest in receiving an HPV vaccine (Dekker, 2006). Parents who believed that their child was not engaged in sexual activity and not at risk for HPV were less likely to endorse HPV vaccination or opposed to it (Brown et al., 2010). In Brewer et al.'s (2007) meta-analysis, perceived likelihood and susceptibility (e.g., “I get sick more easily than other people my age”) were significant predictors of vaccination behavior.

The second factor contributing to the perceived threat from a disease is its perceived severity. In a meta-analysis, perceived severity significantly predicted vaccination behavior (Brewer et al., 2007). In a conjoint analysis of vaccine decision-making among mid-adult women, the severity of disease was one of two main drivers for vaccine acceptability (Stockwell et al., 2011). Poor parental knowledge about the harmfulness of measles infection seemed to be responsible for the low measles vaccination rates in Germany (Schönberger et al., 2009).

The perceived likelihood and severity of a disease are cognitive judgments. Rogers' protection motivation theory (1975, 1983) also includes an affective component with its “threat

appraisal” construct, namely fear. Consistent with this conceptualization, Chapman and Coups (2006) found that anticipated worry mediated the effect of perceived risk on influenza vaccination, and Weinstein et al. (2007) concluded that feeling at risk was a better predictor of vaccination behavior than purely cognitive risk judgments.

3.2.2.2 Attitude toward vaccination

The attitude toward vaccination is a key construct in all theoretical frameworks. The attitude object can be vaccination in general, types of vaccines (e.g., pediatric vaccines), or vaccines against a specific disease (e.g., flu vaccines).

Keane et al. (2005) clustered parents into four vaccination attitude and belief segments, which differed in vaccination rates: vaccine believers (33%), cautious (23%), relaxed (34%), and unconvinced (10%). Gust et al. (2005) identified five parent segments: immunization advocates (33.0%), go along to get alongs (26.4%), health advocates (24.8%), fence-sitters (13.2%), and worrieds (2.6%).

Most studies have been conducted about attitudes toward vaccination against specific diseases, and have generally found strong associations between attitudes, underlying beliefs, and vaccination intentions and behaviors. These associations hold both for persons who are not health care professionals (see, for example, Dekker, 2006; Flood, 2010; Galarce et al., 2011; Raude et al., 2010), and for decisions of health care professionals to get vaccinated (e.g., Maltezou et al., 2010; To, 2010; Betsch & Wicker, 2011).

Attitudes toward vaccination are based on perceived positive (benefits) and negative (barriers) outcomes of vaccination, and their importance. Positive perceived outcomes include the efficacy of the vaccine to prevent the disease, avoid its spread to others, reduce its severity and school and work absenteeism. Negative perceived outcomes include the possibility that the vaccine itself may cause the disease which it should prevent, cause side effects such as transient swelling, redness or fever, alleged but unfounded side effects such as autism or multiple sclerosis¹², weaken the immune system, is painful, costly, and inconvenient (non-financial costs).

One generally finds that persons who perceive more positive and less negative outcomes show higher vaccination intentions and behaviors than persons with less positive and more negative beliefs. For example, parents who delayed and refused vaccines for their children were perceiving fewer vaccine benefits and were more likely to have vaccine safety concerns compared with parents who neither refused nor delayed vaccines (Smith, Humiston et al., 2011; see also Salmon et al., 2005). The belief that products may cause the very harm they

are supposed to prevent violates consumers' trust and represents a "safety product betrayal". Safety product betrayals have been shown to cause negative emotions such as anger, resentment, anxiety, fear, sadness, disgust, and increase the tendency to choose options that provide less overall protection in order to eliminate a very small probability of harm due to safety product betrayal (Koehler & Gershoff, 2003; Gershoff & Koehler, 2011).

The perceived risk of a vaccine can vary across different ethnic groups (Timmermans et al., 2005). Different cultural values can generate divergent perceptions of the risks and benefits of a vaccine (Kahan et al., 2010), and disease prevalence may change the relative importance of efficacy and side effect beliefs. When prevalence is low (high), people worry more about the side effects (efficacy) than about efficacy (side effects) (Lantos et al., 2010).

The perceived financial costs of vaccination are directly influenced by a consumer's reimbursement regime. HPV vaccination initiation was higher for girls with more generous reimbursement regimes, and for girls that were informed personally about the reimbursement rules (Lefevre et al., 2011).

Beliefs about non-financial costs also represent a barrier to vaccination. In a U.S. study, 13% of adults said they were too busy to get a vaccine (National Foundation for Infectious Diseases, no date).

3.2.2.3 Norms

Subjective norms refer to a person's perception of the degree to which important others (referents) think he or she should or should not perform the behavior (e.g., "people who are important to me would approve/disapprove of my having a swine flu vaccination"), and the person's motivation to comply with these referents (e.g., "people who are important to me influence my decision to have a swine flu vaccination", Myers and Goodwin, 2011). Potential referents include governments, medical societies, physicians, family members, friends, and celebrities (e.g., "I heard a TV/movie personality suggest not getting the flu vaccine", Flood et al., 2010). Subjective norms, also called "injunctive norms", have been complemented by "descriptive norms", which refer to perceptions of what others are doing (Smith-McAllen and Fishbein, 2008) (e.g., "most people I know vaccinate their children for the seasonal flu", Flood et al., 2010).

Making vaccination mandatory can raise vaccination rates substantially (Averhoff et al., 2004; Kharbanda et al., 2010; Salmon et al., 2006; Abrevaya & Mulligan, 2011). However, Doyle et al. (2010b) found no correlation between meningitis vaccination rates and vaccination requires across U.S. states. Because most vaccination mandates and recommendations concern

young children and selected groups of at risk adults (diabetes, asthma...), they may contribute to the higher vaccination rates observed among these groups compared to adolescents and adults not at risk. However, because mandatory vaccinations usually are subsidized, the impact of the mandate is confounded with the price impact. Mandatory vaccination may trigger reactance behavior (Brehm & Brehm, 1981), by which people take measures to restore their perception of personal choice.

Whether or not a health care professional recommends vaccination, and the strength of the recommendation has a strong impact on a consumer's vaccination decision. Lack of provider recommendation was the most important factor explaining failure to receive the hepatitis vaccine A (Bardenheier et al., 2003). Among insured women aged 19-26 years, those who discussed the HPV vaccine with their physician and received a recommendation were overwhelmingly more likely to be vaccinated, and the likelihood of vaccination was four times as high when the recommendation was strong compared with when the recommendation was not strong (Rosenthal et al., 2011).

More generally, the belief that people important to self support vaccination is positively associated with vaccination intention and behavior (e.g., Allen et al., 2010; Flood et al., 2010; Myers and Goodwin, 2011). For example, young women who felt their mothers might not want them to be vaccinated were much less likely to complete the 3-dose HPV vaccine series than those who felt their mothers would 'definitely' want them to be vaccinated (Moore et al., 2010). One study found no direct influence of subjective norms on parents' vaccination intentions (Tickner et al., 2010), even though in interviews most parents said that they would attend for immunization because it was "the norm" (Tickner et al., 2007).

Descriptive norms (perceptions of how many friends already had or were considering the HPV vaccine) were the strongest predictor of HPV vaccination adoption stage among college women (Allen et al., 2009). In another study, a student became up to 8.3 percentage points more likely to get immunized if an additional 10 percent of her friends received flu shots (Rao et al., 2007). The bandwagon effect was also evident in an experimental study of flu vaccination intentions (Hershey et al., 1994).

3.2.2.4 Other factors

Additional factors associated with vaccination include anticipated regret, perceived and actual behavioral control, and past vaccination behavior.

Anticipated regret is a cognitively-based negative emotion that arises when people imagine negative outcomes resulting from a decision. Two meta-analyses have shown that

anticipated regret augments the predictive power of the theory of planned behavior (Sandberg & Conner, 2008; Ravis et al., 2009), and several studies have shown that anticipated regret is a significant predictor of vaccination intention and behavior (Connolly & Reb, 2003; Chapman & Coups, 2006; Weinstein et al., 2007; Godin et al., 2010; Morison et al., 2010; Brewer et al., 2010). For example, HPV vaccination initiation was higher among parents who at baseline anticipated greater regret if their daughters got HPV-related disease because they were not vaccinated (Brewer et al., 2010). Anticipated regret was a stronger predictor than cognitively based risk perceptions in two studies (Chapman & Coups, 2006; Weinstein et al., 2007).

People do not always control the performance of a behavior (Ajzen and Fishbein, 2005). Behavioral control has been associated with vaccination intentions (Myers & Goodwin, 2011; Tickner et al., 2010; Petrovic et al., 2011) and vaccination behavior (Prislin et al., 1998; Payaprom et al., 2011).

Past vaccination behavior often predicts future vaccination behavior (e.g., Uddin et al., 2010; Flood et al., 2010). Vaccination against one infection is often associated with vaccination against others (e.g., Galarce et al., 2011; Vaux et al., 2011; Bish et al., 2011; Chor et al., 2011). For example, vaccination against HPV was associated with vaccination against Hepatitis B (Jain et al., 2009), and receiving a recent influenza vaccination was associated with receiving an adult tetanus, diphtheria and acellular pertussis booster (Tdap vaccination (Miller et al., 2011).

3.3 Vaccine prescribers

Vaccine-related behaviors of health care professionals include patient vaccination status review and discussion initiation, vaccination recommendation, and delivery. Physicians differ in their vaccination behavior, and their behavior differs across situations and vaccines. 95% of U.S. physicians reported that they review the immunization status of adolescent patients at health maintenance visits, whereas only 43% reported routinely doing so at illness-related visits (Schaffer et al., 2001). Physicians in Asia initiated 56% of conversations about HPV vaccination, but only 32% of them were proactive initiators, defined as initiating more than 75% of the conversations (Chow et al., 2010). Humiston et al. (2009) segmented physicians by their recommendation behavior into three groups: (1) vaccine advocates, who proactively encourage patients to receive recommended immunizations; (2) vaccine doers, who immunize as a part of their routine or do the service at the request of the patient; and (3) vaccine cautious, who may not offer immunization services or dissuade patients from receiving all recommended immunizations. Only 41% of U.S. primary care physicians strongly recommended a new

herpes zoster vaccine, whereas almost all strongly recommended established vaccines, such as pneumococcal, tetanus, and influenza vaccines (Hurley et al., 2010). While 96% of primary care physicians providing primary care to adults aged 19-64 years stocked at least one vaccine recommended for adults, only 27% stocked all adult vaccines (Freed et al., 2011).

Determinants of physicians' vaccination behavior

Differences in physicians' vaccination behavior have been related to sociodemographic and social psychological variables.

Physician specialty is the socio-demographic variable most often studied. For example, physician specialty (pediatricians vs family physicians) makes a difference for adolescent vaccination practices (Schaffer et al., 2001) and for HPV vaccination (Daley et al., 2010). Physicians who would not recommend HPV vaccination to all eligible patients were more likely to be generalists (Ishibashi et al., 2008). Internal medicine physicians were more likely to stock vaccines for adults aged 19-64 years than family physicians (Freed et al., 2011). Other relevant socio-demographic variables include physician gender and practice characteristics. Female gender of provider was associated with a higher intention to recommend a cervical cancer vaccine (Riedesel et al., 2005). Infant combination vaccines were less likely to be used by smaller pediatric practices, by those with a lower proportion of publicly insured patients, and those with less inclusive state vaccine financing policies (Gidengil et al., 2010).

One study reported a relationship between general social psychological variables and recommendation behavior (Ishibashi et al., 2008). Physicians who would not recommend HPV vaccination to all eligible patients were more likely to have higher intrinsic religiosity and self-described themselves as being conservative. The study also found that pediatricians who recommended the recently launched HPV vaccine to all eligible patients reported earlier adoption of new drugs/vaccines.

The many other social psychological variables that have been used in studies of health care professionals' vaccination behavior can be grouped into three categories. (1) *Medical concerns* reflect the goal to treat consumers in the medically most appropriate way. (2) *Consumer-related concerns* refer to health care professionals' beliefs about consumers' vaccination beliefs, attitudes and behaviors, and how to deal with them. (3) *Financial concerns* represent health care professionals' beliefs about the financial outcomes resulting from their vaccination behavior.

3.3.1.1 Medical concerns

Understanding the disease which is prevented by a vaccine makes pro-vaccination behavior more likely. Several studies have reported a positive association between physicians' perceived knowledge of and experience with a disease and their vaccination intentions and behavior (Chow et al., 2010; Kahn et al., 2005; Riedesel et al., 2005). The perception that the disease represents a significant health problem is also important. Physicians studied by Humiston et al. (2009) indicated that the prevalence, severity, and limited ability to screen for and treat a disease made vaccination more appealing. Physician perception of a high burden of rotavirus disease was associated with very likely adoption of the rotavirus vaccine (Kempe et al., 2007).

Not surprisingly, the most important vaccine characteristics to health care professionals are its efficacy (e.g., coverage of relevant strains, duration of immunity) and safety (Humiston et al., 2009; Riedesel et al., 2005; Zimmerman et al., 1997). A high level of confidence in prelicensure studies of safety was associated with very likely adoption of a newly licensed rotavirus vaccine (Kempe et al., 2007). Non adopters of the pneumococcal conjugate vaccine were significantly more likely than adopters to report concerns about vaccine safety (Daley et al., 2005).

Health care professionals are very attentive to professional vaccination norms. The belief that the A(H1N1) vaccine would be well accepted by health professionals who administer vaccines was a main determinant of Canadian pediatricians' intention to recommend the vaccine to their patients (Dubé et al., 2011). In the U.S., recommendations by organizations such as the American Academy of Family Physicians, American Academy of Pediatrics, Centers for Disease Control and Prevention (CDC), and the Advisory Committee on Immunization Practices (ACIP) significantly increase the likelihood that a vaccine is prescribed to eligible individuals (Riedesel et al., 2005; Kahn et al., 2005; Humiston et al., 2009; Millstein, 1996; Askelson et al., 2010).

A health care professional's intended or actual vaccination of herself, a family member or friend is associated with her vaccination behavior toward other consumers. In Ishibashi et al.'s (2008) study, paediatricians' answers to the question "would you give the HPV vaccine to your own child or the child of a close friend" was highly associated with whether or not they recommended the HPV vaccine to all eligible patients (vs. some or none). Parents often ask physicians: "What would you do if it were your child?" (Humiston et al., 2009).

3.3.1.2 Consumer-related concerns

One reason why physicians do not always recommend vaccination to all eligible consumers is that especially during illness visits urgent consumer concerns dominate (Szilagyi et al., 2005). Another reason may be that physicians segment consumers on the basis of their perceived vulnerability/susceptibility. Zimet et al. (2011) found that physicians gave higher priority for HPV vaccination to women who were single and dating or not dating than to women who were married or in a long-term monogamous relationship, with relationship status functioning as an indicator of the risk for HPV infection.

Some physicians see themselves as proactive advocates for vaccination and others as reactors to consumer requests. 72 percent of high HPV vaccination discussion initiators in Asia agreed with the statement “It is my role to proactively provide advice on preventive health measures to my female patients” compared with 45% of low initiators (Chow et al., 2010). 80 percent of U.S. pediatricians who recommended the HPV vaccine to all eligible patients agreed with the statement “I will recommend the vaccine and try to persuade those who are reluctant” compared with 38 percent of physicians who recommended the vaccine to some/none of patients (Ishibashi et al., 2008). One barrier to advocating vaccination especially when it involves significant out-of-pocket payment is that physicians fear to be seen as “hard-selling an expensive vaccine” (Chow et al., 2010), or as “just trying to give my kid another shot” (Humiston et al., 2009).

Physicians’ vaccination advocacy also depends on their perceived self-efficacy for engaging in vaccination discussions, and actually bringing about the desired consumer behavior. Among the physicians who were high HPV discussion initiators, 76 percent felt “Quite comfortable/very comfortable initiating and conducting conversations with parents about HPV vaccinations”, and 51 percent felt that “a recommendation by their doctor will improve the likelihood of a mother getting her daughter vaccinated” compared with 53 percent and 36 percent respectively among the low discussion initiators (Chow et al., 2010). Daley et al. (2006; 2010) found that the perceived need to discuss sexuality prior to recommending HPV vaccine, and the belief that parents of 11-12 year old would be more likely to refuse than parents of 16-18 year olds were associated with a lower likelihood and strength of recommending HPV vaccine to 11-12 year old female patients.

3.3.1.3 Financial concerns

Health care professionals are also concerned with the financial outcomes of their vaccination behaviors. The fee for vaccine administration may not adequately compensate them for the time spent (Humiston et al., 2009).

Additional financial concerns arise when physicians also dispense vaccines. In the U.S., most physicians dispense both vaccines which are purchased by the government and private-sector vaccines which are purchased by physicians in advance of patient demand. The latter involve costs for ordering and managing the stock, investment in refrigerators (or freezers for some vaccines), and financial risk (Shen, Rodewald & Birkhead, 2009). These financial concerns can represent important barriers to physician involvement in vaccination (Gidengil et al., 2009, 2010; Hurley et al., 2010; Freed et al., 2011; Campos-Outcalt et al., 2010; Freed, Cowan & Clark, 2008; Coleman et al., 2009).

3.4 Organizations issuing vaccination recommendations

The number of vaccine-treatable diseases and licensed vaccines has increased significantly over the last decades. Three types of organizations help consumers, physicians, governments and private insurers define priorities: national technical advisory groups (NITAGs), national medical societies, and the World Health Organization (WHO).

3.4.1 National technical advisory groups (NITAGs)

National technical advisory groups (NITAGs) are committees which develop recommendations on new vaccine introduction and vaccination schedules to national governments (Gessner et al., 2010).¹³ The NITAG in the US is the Advisory Committee on Immunization Practices (ACIP). Established in 1964, ACIP recommends licensed new vaccines to be incorporated into the routine immunization schedule and reviews older vaccines to consider revising its recommendations, among other tasks. ACIP guidance is sought routinely whenever a new vaccine is licensed, or when there is a change in licensed specifications. In addition, ACIP designates those vaccines to be included in the federal Vaccines for Children (VFC) Program, which pays for vaccine administration to almost 50% of American children under 6 years of age (Smith, Snider & Pickering, 2009; Smith, J.C., 2010).

ACIP recommendations are made primarily on the basis of the burden of disease, vaccine effectiveness and safety. Formal economic evaluation, e.g., through cost-effectiveness analysis, also plays a role in ACIP decision-making (Smith, J.C., 2010). ACIP recommendations are subject to approval of the Director of the Centers for Disease Control and

Prevention (CDC), which are part of the US Department of Health and Human Services (HHS). Except for the Vaccines for Children (VFC) designation, ACIP has no direct role in vaccine financing, purchasing and administration. These decisions are made by other federal agencies, state health departments, and private insurers. However, ACIP recommendations are generally regarded as national policy, followed by public and private insurers, and set the standard of practice for physicians (Smith, J.C., 2010; Berndt et al., 2009).

Well established NITAGs can be found in all regions of the world.¹⁴ In an international survey (Bryson et al., 2010), the presence of a NITAG was reported in 61% of 147 countries. But only 26% of the NITAGs met all indicators of a well functioning NITAG¹⁵. The factors most widely considered by NITAGs when making recommendations are vaccine safety (100% of countries), disease burden in the home country (99%), public health/epidemiology (95%), financial aspects such as cost-effectiveness (91%), public perception of the disease (59%), and recommendations from NITAGs in other countries (55%). Vaccine effectiveness was the most widely used factor (98%) in non-European countries (Bryson et al., 2010).

3.4.2 National medical societies

Many national medical societies issue vaccine recommendations. An internet search of recommendations on HPV vaccination identified 4 issuing organizations in the US, 5 in Canada, and 5 in Spain, among others (Marquez-Calderon et al., 2009). Recommendations by medical societies have a significant impact on physicians' vaccination behavior (see section 3.3.1.1).

National medical societies can also influence recommendations issued by NITAGs. For example, the US ACIP includes liaison representatives from medical societies as non-voting committee members.¹⁶ They are required to bring the perspective of their organizations to the ACIP and to disseminate ACIP's recommendations back to their membership. ACIP recommendations may be developed and issued jointly with medical societies (Smith, Snider & Pickering, 2009; Smith, J.C., 2010).

3.4.3 The World Health Organization (WHO)

The World Health Organization (WHO), an agency of the United Nations (UN), defines global immunization goals and plays an important role in all stages of the vaccine value chain. WHO supports vaccine and immunization R&D through partnerships (e.g., the Meningitis Vaccine Project (MVP), Butler, 2010), issues recommendations to help countries decide which vaccines to introduce, sets technical specifications that form the basis of guidelines for vaccine

production and prequalification, prequalifies vaccines, provides technical support to countries for the introduction of new vaccines, estimates the burden of vaccine-preventable diseases, monitors countries' immunization policies, and plays a key role in managing pandemics such as the 2009 H1N1 pandemic.

For vaccine marketers targeting middle to low-income countries, WHO vaccine recommendations and prequalifications are of particular importance.

3.4.3.1 WHO vaccine recommendations

WHO regularly produces and updates position papers on available licensed vaccines of public health interest, with recommendations on the optimal use of the vaccines, mainly for national public health officials and immunization program managers. The position papers are developed by the Strategic Group of Experts (SAGE), which consists of 15 international experts. SAGE takes into consideration issues such as disease epidemiology, clinical characteristics (e.g., clinical management of disease), vaccine and immunization characteristics (e.g., efficacy, population impact of vaccine; safety; vaccine availability and supply), economic considerations (e.g., cost-effectiveness and affordability of immunization), health system opportunities and the existence of, and interaction with, other existing intervention and control strategies (Duclos et al., 2011; see also Milstien et al., 2010). SAGE global recommendations are reviewed and adapted at the regional level by WHO regional offices (Levine et al., 2011).

WHO recommendations are reported to be central to the vaccine policy process especially in developing countries and international funding agencies such the GAVI Alliance (Duclos et al., 2011). 78 (89%) out of 88 NITAGs reported using WHO position papers when making recommendations (Bryson et al., 2010). However, an analysis of country adoption of *Haemophilus influenzae* Type b (Hib) vaccine found no influence of WHO position papers on country time to adoption (Shearer et al., 2010).

3.4.3.2 WHO prequalification of vaccines

The UN Agencies UNICEF and PAHO, which are important purchasers of vaccines, only purchase vaccines which have received WHO prequalification, the main goal of which is to assure that a specific vaccine meet international standards of quality, safety and efficacy. A prerequisite for prequalification of a specific vaccine is that the national regulatory agency of the country of manufacture meets the WHO criteria for a “functional” regulatory authority. As of March 2011, 22 countries had such functional regulatory authorities, China being the most recent addition.¹⁷

Vaccines which have been prequalified can compete for UNICEF and PAHO business. Because WHO prequalification is a quality signal, many individual countries use the list of WHO prequalified vaccines when purchasing directly from vaccine manufacturers (International AIDS Vaccine Initiative, 2008a). WHO Prequalified vaccines are subject to routine site audits and can be delisted in case the requirements for prequalification are not met.¹⁸

3.5 Vaccine purchasers

3.5.1 Public purchasers

In public markets, the decision to purchase a vaccine, its procurement, and its funding are often under the responsibility of different organizations.

3.5.1.1 The decision to purchase a vaccine

The decision to purchase a vaccine can be made by national and regional authorities. For example, the U.S. NITAG ACIP can add a vaccine to the federal VFC program, which funds vaccines for low-income children. At the same time, individual states can decide to purchase a vaccine for children not eligible for VFC, or to purchase a vaccine not funded at all by a federal program (Orenstein et al., 2007; Lindley et al., 2009; Freed & Cowan, 2002).

A vaccine which has secured a recommendation from a country's NITAG has a much greater chance of being purchased by that country's public purchasers than one without. In most countries, NITAG recommendations are advisory, but in some cases they are legally binding, as when ACIP designates a recommended vaccine for VFC funding, and in the UK (Hall, 2010).¹⁹ In Australia, a positive NITAG recommendation is a necessary condition for government funding of a new vaccine (the government cannot fund without a positive recommendation), but is not sufficient (the government is not obliged to fund when the recommendation is positive) (Nolan, 2010).

Public opinion and political pressure can influence public vaccine purchasing. For example, the initial negative recommendation concerning the HPV vaccine Gardasil by the Australian NITAG immediately unleashed widespread opposition, prompting the Health Minister and the Prime Minister to express their support for funding. Less than four weeks later, the NITAG reversed its recommendation from negative to positive, and Gardasil obtained government funding (Roughead et al., 2008).

Affordability of a vaccine is another important factor in public vaccine purchasing. Budget limitations were the most common reason for lack of implementation of NITAG recommendations reported in a study of 15 NITAGs (Gessner et al., 2010). The decision by a public purchaser to purchase a new vaccine essentially implies a commitment to endless funding, since (save for smallpox) infectious diseases are never fully eradicated. To free up budgetary resources and create “fiscal space” for new vaccines, public purchasers put pressure on the prices of older vaccines. Thanks to their greater budgetary resources, high-income countries have historically adopted new vaccines rapidly, whereas in low-income countries vaccine uptake was delayed by 15-20 years despite their higher burden of disease (Levine et al., 2011).

A recent 147-country multivariate analysis of the time to adoption of the Hib vaccine showed that, compared to high-income OECD countries, time to adoption was longer for other countries. Other variables associated with a longer time to adoption were a higher vaccine price and higher GAVI co-financing uncertainty. Variables associated with a shorter time to adoption were eligibility for GAVI financial support, having neighbor countries who already have adopted the vaccine, and a higher degree of democracy (Shearer et al., 2010).

3.5.1.2 Vaccine procurement by public purchasers

Authorities may procure a vaccine directly from the manufacturer, through a public procurement agency which pools purchases to obtain more favorable conditions, or they may let health care professionals manage procurement. Public procurement agents may operate at the national level, pooling purchases from sub-national authorities, or at a supranational level, pooling purchases from several countries.

In the U.S., most vaccines for public immunization programs are procured by the CDC on behalf of sub-national jurisdictions. The original “winner take all” contracts were later replaced by multiple-supplier contracts that guaranteed the largest market share to the lowest bidder, followed by the current approach, under which CDC negotiates each year federal contract prices for all public immunization programs receiving CDC funds.²⁰ The contract prices, published together with the manufacturers’ list prices on the CDC website, range from 4 to 67 percent below list prices (Centers of Disease Control and Prevention, 2011). States and other jurisdictions purchase vaccines through the CDC at the federal contract price. Individual US states also purchase vaccines directly in some circumstances.²¹ When the CDC has contracted different vaccines targeting the same disease, states are free to choose from among them (Institute of Medicine, 2003). Some states select a subset among the competing brands to

reduce system complexity and costs, while others leave the choice up to the health care professionals (“provider choice”), hoping this will raise the willingness of private practices to provide public vaccines (Freed and Cowan, 2002).

The UK National Health System (NHS) has a dual system for procuring vaccines for its universal vaccination programs. Vaccines for the routine childhood program are procured centrally by the Department of Health and distributed directly to GPs. Vaccines for the seasonal flu vaccination program, however, are procured by GPs, who receive reimbursement for the cost of the vaccine plus a fee for procuring the vaccine. The NHS is currently considering central procurement of seasonal flu vaccine, a move which it estimates would reduce vaccine costs by 35% and procurement administration costs by 76% (Department of Health, 2011).

The UN’s UNICEF Supply Division and the Revolving Fund of the Pan American Health Organization (PAHO) are the two most important supranational vaccine procurement agencies.²² The UNICEF Supply Division is the major procurer of vaccines for low-income countries²³, procuring immunization supplies on behalf of around 80-100 countries annually, reaching 58 percent of the world’s children. In 2010, UNICEF procured around 2.5 billion doses of vaccines, at a value of \$750 million.²⁴ UNICEF procures only vaccines that have been WHO prequalified²⁵. To promote vaccine security (the uninterrupted, sustainable supply of affordable vaccines of assured quality) UNICEF tries whenever possible to procure each vaccine from several manufacturers instead of pursuing a “winner takes all” policy (International AIDS Vaccine Alliance, 2008). Countries or donors pay for vaccines upfront by depositing the needed funds with UNICEF, which provides manufacturers with demand forecasts, and enters into multi-year supply arrangements (International AIDS Vaccine Initiative, 2008b). A recent change in policy from posting only average prices to posting prices for individual vaccines²⁶ from manufacturers having given permission to do so revealed significant price differences. Some companies disclosed their prices, others refused, but all agreed not to disclose their cost structures. UNICEF hopes that the increased price transparency will lead to a more competitive market and lower prices, especially for newer vaccines (McNeill Jr., 2011).

PAHO’s Revolving Fund is a mechanism for the joint procurement of vaccines, syringes, and related supplies for PAHO’s 35 member states.²⁷ In 2007, PAHO purchases amounted to about \$225 million, with Brazil, Argentina, Colombia and Venezuela being the top four purchasers by value (International AIDS Vaccine Initiative, 2008b). PAHO procures

only vaccines that have been WHO prequalified or approved in the US, EU, Canada, Korea, or Australia. Manufacturers are selected based on the lowest price, the quantity offered, and the producer's quality and service record. To guarantee supply, PAHO contracts with at least two manufacturers. PAHO publishes weighted average vaccine prices per dose²⁸ and claims that a country that purchases through PAHO can save at least 14% compared to purchasing directly from the producer (Pan American Health Organization, 2010).

3.5.1.3 Funding of public vaccine purchases

Public purchasers can finance vaccines with government funds (national and sub-national fiscal resources) or with funds obtained from donors.

The share of government financing of vaccines used in routine immunization was estimated at 94% in the Americas, 92% in Europe, 84% in the West Pacific, 79% in the Eastern Mediterranean, 53% in Africa, and 49% in South East Asia. Having a specific line item for vaccines in the national health budget, as was the case for 86% of countries in 2006, was associated with increased governmental budget allocations for vaccines and routine immunization financing (Lydon et al., 2008). Government-funding based on entitlement programs can accommodate the cost of new vaccines more easily than programs which depend on annual discretionary appropriations. For example, in the US, vaccine funding under the VFC entitlement program increased by nearly 400% from fiscal year 2000 to fiscal year 2008, compared with a mere 42% increase for the discretionary Section 317 program (Lindley et al., 2009).

Donor financing of vaccines is particularly important in low income countries, where total per capita government spending on health averaged about \$15 in 2008 (Saxenian et al., 2011), while the cost of vaccinating a child fully through age 18 at the US federal contract price amounted to \$1,105 for boys and \$1,407 for girls (Lindley et al., 2009). Vaccine expenditures without donor contributions in low income countries would have accounted for 4.2% of government spending on health in 2010, rising to 6.3% in 2015. By comparison, spending on vaccines in Latin American countries, which tend to be early adopters of new vaccines, amounts to slightly less than 1 percent of government spending on health (Saxenian et al., 2011).

The GAVI Alliance, a public-private partnership between the Bill & Melinda Gates Foundation, WHO, UNICEF and the World Bank, created in 2000 to promote immunization in the poorest countries, is the most important international non-governmental vaccine funding source. GAVI pools donor contributions, and funds approved applications for the purchase of

new and underused vaccines by eligible countries. Only countries with a per capita gross national income (GNI) equal to or less than US\$ 1,500 are eligible. To ensure that GAVI funding comes in addition to and does not substitute or “crowd out” current funding, only vaccines that are not already introduced in the routine schedule and already financed are supported.²⁹ Procurement of GAVI-financed vaccines by UNICEF, the main procurement channel of GAVI³⁰, reached about \$360 million, representing 42% of UNICEF’s total vaccine procurement.³¹ In countries which introduced vaccines with GAVI support, GAVI’s share of the 2008-2010 immunization financing per infant was projected at 46%, followed by governments (38%), and multilateral and other donors (16%) (Zuber et al., 2011).

Following the June 2011 pledging conference, GAVI’s total available resources for the period 2011-2015 amount to \$7.6 billion.³² Through its various activities, GAVI has significantly raised the attractiveness of low income markets by increasing the size and reliability of demand forecasts, which are key inputs for manufacturers’ investment decisions. GAVI’s challenge for the future is to help low income countries increase national ownership and financing of immunization, while continuing to raise the funds necessary to support the countries which will still need external support (Saxenian et al., 2011).

3.5.2 Private purchasers

In the US and many other countries, physicians dispense vaccines, in addition to prescribing and administering them. In countries which do not allow physician-dispensing, as is the case in France, patients must make a first physician visit to obtain a prescription, get the vaccine from a pharmacy, take the vaccine home - hopefully not during a long trip on a hot day - stock it in their refrigerator, and then return with the vaccine to the physician for administration.³³

Physicians are the main private market purchasers in countries which allow physician-dispensing. Other private market purchasers include pharmacies, hospitals and - for influenza vaccines - employers.

3.5.2.1 The decision to purchase a vaccine

Vaccine-dispensing physicians usually have both public and private vaccines in their refrigerator. Public vaccines are purchased by the authorities and made available to physicians at no cost. Private vaccines are purchased by physicians and involve the economics typical of pharmacies and other types of distributors. Key concerns include consumer demand, the profit margin, asset turnover, financial leverage (asset/equity ratio), and financial risk.

Drivers of the private consumer demand for a vaccine include the size of the population for which the vaccine is licensed, whether the vaccine is recommended by the country's NITAG and for which population, consumers' out-of-pocket costs, and the promotional effort for vaccination and the vaccine brand, in case there are competing brands. The speed, breadth (percent of the eligible population) and extent of insurance coverage (percent of the total retail price which is reimbursed) is an important factor for the uptake of a new vaccine (Shen, Rodewald & Birkhead, 2009).

Many US physicians complain about the profit margin from vaccines (see Section 3.3.1.3). In one study, one or more practices reported that the vaccine purchase price exceeded the most common payer reimbursement for 15 out of 21 vaccines (Freed et al., 2008). In another study, the net profit margin (vaccine revenues minus vaccine expenses) was higher for patients with private insurance reimbursement than for Medicaid-enrolled patients, many of whom generated a negative net margin (Hunsaker et al., 2009).

Because asset turnover is reduced when physicians carry several brands of vaccines that target the same disease, physicians prefer to concentrate their purchasing on one of the brands.³⁴ Financial leverage is influenced by the payment terms of the vaccine supplier compared with the speed of insurance reimbursement. Financial risk derives mainly from demand and supply uncertainty. When the amount of vaccines purchased exceeds demand, physicians may experience high inventory, obsolescence, and expiration costs, the risk being especially high for seasonal vaccines such as influenza, and for new vaccines. Purchasers attempt to shift the risks of over-stocking by requesting a returns policy. Such a policy requires monitoring by a manufacturer, to ensure that his vaccine is not the “first in but last out” at the purchaser.

3.5.2.2 Vaccine procurement by private purchasers

Private purchasers can procure vaccines directly from vaccine manufacturers, purchasing cooperatives/buying groups, or distributors. A US study found a wide range of prices paid by physician practices for the same vaccine product, with the difference between the highest and lowest price exceeding 100% in several cases. More than half of the practices participated in a purchasing cooperative for at least some of the vaccines they purchased. Practices participating in purchasing cooperatives, medium and large practices, and those located in metropolitan statistical areas (MSAs) tended to purchase at lower prices. The average private-practice prices were higher than the federal contract price for 20 out of 21 vaccines studied (Freed et al., 2008).

3.5.2.3 Vaccine funding of private purchases

A vaccine which is not publicly purchased can be fully funded through private insurance, partially funded by private insurance with cost sharing by consumers, or funded entirely out-of-pocket by consumers.

In the US, ACIP-recommendations are the main factor driving vaccine coverage decisions for children and adolescent vaccines by private insurers in the US (Hunsaker et al., 2009). ACIP-recommendations also influence private insurance coverage of vaccines recommended for adults. However, insurance plans require more cost sharing for adults than for children and adolescents (Orenstein et al., 2007; Shortridge et al., 2011).

Vaccine coverage decisions by private insurers may also result from legal mandates. For example, New York state requires that health plans cover recommended childhood vaccinations and that the coverage must be “first dollar”, that is, deductibles, coinsurance, or copayments cannot apply (Benatar et al., 2010). A key provision of the US 201 Patient Protection and Affordable Care Act (“Affordable Care Act”) which increases mandatory vaccine coverage is expected to reduce financial barriers to vaccinations for many consumers (Adult Immunization Working Group, 2011; Tan, 2011).³⁵

3.6 Vaccination advocates and opponents

Vaccination beliefs, attitudes and behaviors are also influenced by individuals and organizations other than the preceding types of stakeholders. Their aim can be to promote vaccination or, on the contrary, oppose it.

HVP vaccination provides an example of pro- and anti-vaccination advocacy. Women in Government, a U.S. organization for elected women in state governments focused on public policy issues, particularly those affecting women, played an important advocacy role for HPV vaccination (Baron, 2008). In Europe, a number of civil society organizations actively supported the HPV vaccination agenda (Laurent-Ledru et al., 2011). Opponents in the U.S. were found mainly in conservative Christian groups who feared that HPV vaccines would spur promiscuity and undermine abstinence (Guyon, 2005; Baron, 2008).

Opposition to vaccination has a long history, starting in the 18th century with the first vaccine (Poland & Jacobson, 2011; Spier, 2001; Offit, 2011). Concerns about vaccine safety are fueled by generally unsubstantiated anti-vaccination writings, which can lead to vaccination refusals and subsequent disease resurgence (Leask et al., 2010; Larson et al., 2011). A well-known case is a 1998 article in *The Lancet* claiming that the measles-mumps-rubella (MMR)

vaccine causes autism. The article was formally retracted and recently shown to have been an elaborate fraud (Deer, 2011; Godlee et al., 2011).

4 Vaccine marketing decisions

4.1 Deciding where to compete

The main dimensions for segmenting the vaccine market are disease targets, consumers, countries, and products (technologies).

The CDC website lists 26 different diseases which are preventable with currently existing vaccines.³⁶ Preventive vaccines against at least another 12 diseases are under development (Business Insights, 2009).

The potential consumers for each vaccine are usually segmented by age (e.g., infants, children, adolescents, adults) and/or other indicators of increased risk for the disease (e.g., injecting drug users for hepatitis B). Country/region is an additional important segmentation variable for consumers because of regional variations in disease risk, vaccine efficacy, and other country/region characteristics.

Differences in vaccine products, finally, are a fourth dimension for structuring the vaccine market. Vaccines can be classified by product technology (e.g., live attenuated (weakened) organisms, killed (inactivated) whole organisms), etc.), process technology (e.g., egg-based vs. cell-based production), delivery method (e.g., injectable, intranasal, etc.), number of diseases targeted (single- vs. combination vaccines), valence (mono vs. multi-valent vaccines), and other product characteristics.

The attractiveness of the various disease / consumer / country/region / product segments is typically assessed through variables including segment size and growth, and segment profitability drivers such as competitive rivalry, buyer power, entry barriers, and threats from substitutes (Porter, 1980). Vaccine-specific indicators underlying assessments of segment size and growth include population/birth cohort size and growth, actual and perceived burden of disease, per capita income and its growth, immunization programs (against what diseases? for which consumers? how funded?), and relevant characteristics of the health care delivery system (e.g., physician and nurse density, and cold chain characteristics).

4.2 Creating competitive advantage

To achieve a competitive advantage in the segments in which a firm competes, it must drive a wider wedge between willingness to pay and costs than its competitors (Ghemawat,

2010). Differentiation, low-cost, and dual advantage are the three generic strategies through which firms attempt to achieve a competitive advantage (Porter, 1980; Ghemawat, 2010).

Multinational vaccine manufacturers tend to pursue differentiation strategies. Product-based differentiation seeks to increase vaccine efficacy, safety for consumers and vaccinators, convenience of administration (e.g., one instead of multiple doses; combination vaccines to reduce the number of visits and injections per person; administration devices such as intradermal syringes for Sanofi Pasteur's Intanza flu vaccine), tolerability (e.g., no or less painful injection), and reduce logistics requirements (e.g., less stringent cool chain requirements; longer duration of conservation).

Among the non-product based differentiation tools reliability of supply is particularly important. There is a history of vaccine shortages, rationing, and black markets, due both to production failures associated with the complexity of vaccine manufacturing and the small number of suppliers for many vaccines (Scherer, 2007).³⁷ In some countries, governments expect that multinational companies invest in local facilities (e.g., formulation, fill & pack plants) and/or technology transfers. Responding to these expectations may provide a differentiation advantage. Services provided to physicians and distributors are other avenues to achieving differentiation.

Differentiation fails if the costs associated with differentiation are high relative to the incremental willingness-to-pay. Investments in local facilities and other services may generate incremental costs, which may be higher than the incremental willingness-to-pay. Product improvement efforts may be similarly misguided. For example, believing that its nasal spray influenza vaccine FluMist (direct cost \$15 per dose), would be valued highly in comparison with traditional flu injections (direct cost \$3.50 per dose), MedImmune priced FluMist at \$46 per dose, triple the price of a traditional flu shot, invested \$43m in measured media for the launch season, and produced 4 million doses. Actual sales amounted to about 400,000 doses (Thomaselli, 2004; Calkins, 2004).

Differentiators are also threatened by competitors who attempt to match the differentiator's offering, while operating at lower costs. Vaccine manufacturers based in low-cost countries who have achieved WHO prequalification represent such a threat to multinational vaccine manufacturers' sales in low-income countries, and progressively also in middle-income countries.

Some low-cost vaccine manufacturers may enjoy a competitive advantage vis-à-vis multinational firms even if they do not achieve willingness-to-pay parity as long as their cost

advantage is larger than their willingness-to-pay gap. Their cost advantage allows them to compete successfully in low income countries where buyers value a low price more than product- and non-product performance differences. Multinational manufacturers attempt to counter this threat through acquisitions of and partnerships with low cost manufacturers.

4.3 Product and branding strategy

Compared with therapeutics, the size of vaccine product lines is modest even for the largest vaccine manufacturers. GSK, the number one vaccine firm, had only “over 30” approved products in 2010 (Andrews, 2011). Product lines grow in size through the addition of vaccines against new disease targets, and by developing differentiated versions of existing vaccines.

Four factors encourage vaccine differentiation. (1) Differences in vaccine efficacy across consumer segments: because standard flu vaccines are less effective for elderly, Sanofi Pasteur launched High Dose FluZone for the elderly. (2) Differences in vaccine efficacy across regions: for example, a Hib vaccine effective in Finland was not in Alaska, and Chilean infants raised three times higher antibody responses than did children in Belgium (Moxon & Siegrist, 2011). (3) Diversity in preferences for other product features, e.g., needle-phobia is higher among children than adults. (4) Diversity in ability to pay: for example, Sanofi Pasteur offers three vertically differentiated pertussis vaccines - a whole cell pertussis vaccine; a 2-component acellular pertussis vaccine; a 5-component acellular pertussis vaccine - at different prices in different markets. Pfizer markets Prevnar, which protects against 7 serotypes, and Prevnar 13 with protection against 13 serotypes, at different prices. Moreover, price discrimination can be more easily sustained with product differentiation, and differentiated products can justify higher prices. For example, Sanofi Pasteur’s High Dose FluZone and IntraDermal flu vaccine are sold at a premium compared to standard vaccines in the U.S.

The main obstacle to vaccine differentiation is the increase in complexity and cost for vaccine manufacturers and buyers. Doubling the number of vaccines in a country and introducing single-dose vials in addition to multi-dose vials (for safety reasons and to reduce the waste that occurs when a partially used vial has to be discarded) is estimated to increase vaccine storage needs by 500 percent or more (Kaufmann et al., 2011). Product differentiation also increases costs for vaccine-dispensing physicians, because ordering, stocking and handling several vaccines instead of one significantly increases costs and risks. This explains why physicians prefer vaccines that are licensed and recommended for a broad group of consumers over products with a narrower license. For example, GSK’s adolescent and adult DTP booster

vaccine Boostrix, indicated for individuals 10 years and over, represents a threat to the leadership of Sanofi Pasteur Adacel's, which is limited to individuals between 11 and 65 years.

Global branding of vaccines depends on companies' manufacturing strategy. Because brand names are linked to regulatory dossiers which, in turn, are linked to manufacturing sites, the same vaccine produced at a different site must carry a different brand name. For example, GSK markets two flu vaccine brands – Fluarix and Flulaval – each of which is produced at a different manufacturing site. Global branding therefore requires that a vaccine sold throughout the world be produced at only one manufacturing site.

The big five vaccine manufacturers pursue different branding policies. GSK, Merck and Pfizer-Wyeth use their corporate brand, plus product brands. Novartis uses Novartis (in large letters) Vaccines (in small letters) as a master brand (Aaker, 2004), plus product brands. Sanofi Pasteur is Sanofi's master brand for vaccines. It combines the corporate brand (Sanofi) with the product family brand Pasteur, which leverages the valuable equity of Louis Pasteur, the creator of the first vaccine against rabies and anthrax. GSK's product names provide a horizontal link across all vaccine products (Keller, 2008) through the use of the suffix “rix”, as in Cervarix (HPV vaccine), Rotarix (rotavirus vaccine), and Havrix (hepatitis A vaccine). Sanofi Pasteur uses the suffix “cim” for its 2-component acellular pertussis (acP) vaccines (Pentaxim, Tetraxim, Hexaxim), and “cel” for its 5-component acP vaccines (Adacel, Daptacel, Pentacel).

4.4 New vaccines

4.4.1 New vaccine development

One direction for new product development in the vaccine industry is to develop vaccines for new disease targets. The second direction for new vaccine development is to improve existing vaccines in terms of efficacy, safety, convenience, tolerability, manufacturability, transportability and storability, and cost and ease of delivery.

When target antigens are constant and do not vary over time, as is the case for MMR, yellow fever, tetanus, diphtheria, and Hib, existing vaccines maintain their efficacy. Improvements of these vaccines are therefore less frequent and focus on attributes other than efficacy. But when there are variations in the target vaccine antigens, the efficacy of existing vaccines may change. For example, influenza A antigens vary from one season to the next. To maintain efficacy, vaccines against this disease and others with similar dynamics require periodic changes. A disease like HIV with its high and unpredictable variation of HIV antigens represents a major challenge for the development of HIV vaccines (Moxon & Siegrist, 2011).

The development of vaccines with sustained efficacy against dynamic target antigens would represent a major scientific breakthrough with significant commercial potential.

Berndt et al. (2009) compared development times, success probabilities, and development costs of vaccines and other pharmaceuticals. Development times for vaccines have been shorter than for other types of pharmaceuticals, while mean vaccine FDA approval times have been longer, particularly for follow-on vaccines. But the average capitalized costs are probably similar. Light et al. (2009) estimated the capitalized R&D costs (without taking into account the cost of failures) of Merck's RotaTeq rotavirus vaccine at \$205-644 million, and of GSK's Rotarix at between \$172-551 million.

Because of their impact on public health, governments are more strongly involved in the development of vaccines than of therapeutics. The 2010 U.S. National Vaccine Health Plan defines as one of its goals the development of new and improved vaccines, requiring the prioritization of new vaccine targets of domestic and global public health importance (U.S. Department of Health & Human Services, 2010). The U.S. Biomedical Advanced Research and Development Agency (BARDA) issues requests for proposals for prioritized vaccines that include Target Profile Specifications (TPP) including desired indications, formulations, dosing, delivery mechanisms, packaging, storage and transport, shelf life, or other considerations (Institute of Medicine, 2010).³⁸

Governments promote vaccine development through “push” and “pull” mechanisms. “Push” mechanisms subsidize costs, whereas “pull” mechanisms increase demand. Push mechanisms include direct financing of vaccine development, facilitating research, harmonizing regulatory requirements, and tax credits for vaccine research (Lieu et al., 2005).³⁹ Advance Market Commitments (Kremer, 2001a, b; Snyder et al., 2011), which guarantee that manufacturers will be able to recoup production costs, as well as investments in development, manufacturing capacity, and production costs, are an example of a “pull” mechanism.

Four models of organizing vaccine research and development have been identified (Wilson, 2007): (1) predominantly private sector development; (2) public sector vaccine design, and transfer to the private sector for clinical trials and production; (3) predominantly public sector development; and (4) coordination by a non-profit entity, for example, by public-private product development partnerships (PDPs). PDPs are involved in efforts to develop vaccines against AIDS (e.g., the International AIDS Vaccine Initiative, IAVI), malaria e.g., the Malaria Vaccine Initiative), and tuberculosis (e.g., the Aeras Global TB Vaccine Foundation) (Institute of Medicine, 2010; see also Eskola & Kilpi, 2011).

4.4.2 Launching a new vaccine

Key goals when launching a new vaccine in a country are: (1) recommendations by the country's NITAG and the medical societies, which are most important to the vaccine core prescribers; (2) WHO recommendation and pre-qualification; (2) favorable pricing and reimbursement conditions by public and private third-party payers; (3) strong recommendations by physicians to eligible patients, and (4) consumer willingness to be vaccinated with the vaccine.

NITAGs start working on future vaccines several years before the expected licensing date. For example, ACIP formed an HPV Vaccine Workgroup in 2004, two years before the first HPV vaccine Gardasil was licensed in June 2006 (Shefer et al., 2008). Most NITAGs and WHO collect and review data on the epidemiology, burden of disease, vaccine efficacy, safety, and cost-effectiveness (see Sections 3.4.1 and 3.4.3). A vaccine manufacturer can influence this process by providing appropriate data, build epidemiological, health-economic and other economic models, and generating evidence of vaccine efficacy, safety, and other relevant aspects. Obtaining favorable recommendations from medical societies similarly requires that the manufacturer interact with these societies prior to the launch and provide them with relevant information.

The goal is to obtain recommendations as quickly as possible following the licensing, because this facilitates price and reimbursement discussions with payers. For example, Merck succeeded in obtaining a favorable ACIP recommendation for Gardasil in the same month as the FDA approval. For vaccines destined mainly for countries procuring via UNICEF and PAHO, obtaining a WHO recommendation and pre-qualification rapidly is essential. It is not relevant for vaccines destined for the U.S., EU, and other high income countries.

Obtaining a high price and favorable reimbursement conditions from public and private third-party payers is the next challenge. This requires a good understanding of the decision process, who the key influencers are (e.g., through social network analysis as illustrated by Conway et al., 2008), their decision criteria and perceptions of the burden of disease, the vaccine and the manufacturer. Like for NITAG recommendations, the goal is to arrive at satisfactory price and reimbursement agreements as rapidly as possible after licensing.

A new vaccine which has obtained recommendation by the NITAG and key medical societies, favorable reimbursement conditions, namely no consumer cost sharing, and physician reimbursement that promises profits from dispensing and administering the vaccine, is in a good position to trigger strong physician recommendations to eligible consumers. Including the

vaccine in the metrics used by payers to measure physician performance can generate additional physician support. According to Freed et al. (2011), one of the reasons why the vast majority of primary care physicians stocked the pneumococcal polysaccharide (PPSV23) vaccine compared with the much lower stocking rate of most other adult vaccines was that it was one of two vaccines included as part of the Healthcare Effectiveness Data and Information Set (HEDIS), a tool used by most US health plans to measure physician performance.

Last not least, the new vaccine needs to be accepted by consumers. Making vaccination with a new vaccine mandatory might be seen as the most effective way to speed up its consumer acceptance. This is what Merck attempted to achieve through extensive lobbying when they launched Gardasil. However, faced with growing criticism, they suspended their lobbying effort six months after launch (Rosenthal, 2008). Schwartz (2010) recommends that vaccine mandates should be considered only after a new vaccine is well established and widespread support exists, which traditionally has taken at least five years.

4.5 Vaccine pricing

Like for other pharmaceuticals (Frank, 2001), for vaccines the “law of one price” holds neither within nor across countries. Public buyers in the U.S. benefit from lower prices than private buyers, and even among private buyers there is enormous variation in the prices paid by different physician practices for the same vaccine (Freed et al., 2008).

Prices for the same vaccine can also vary greatly across countries. For example, among seven high-income countries the launch price for Gardasil was highest in Germany at \$527, followed by \$429 in Switzerland, \$360 in the US, \$359 in Denmark, \$335 in Canada, \$315 in Australia, and lowest in New Zealand at \$292 (Haas et al., 2009). Low and middle income countries procuring vaccines through UNICEF/GAVI and PAHO only pay a fraction of the public sector US federal contract price. For example, the UNICEF/GAVI prices per dose for four vaccines ranged from 2% to 12% of the U.S. federal contract price (Nguyen et al., 2011).

Some of the price differences may be due to differences in costs. Different contractual arrangements concerning logistics, product liability, returns policy, payment, length of contract, and guaranteed volumes may indeed engender cost differences.

Price differences can also represent price discrimination, also called differential pricing or tiered pricing. Tiered pricing exploits differences in price elasticity resulting from differences in buyer power, willingness to pay, and ability to pay. The lower U.S. federal contract price compared to the private sector price, and the lower prices of practices participating in purchasing cooperatives purchase compared to practices buying directly from

manufacturers (Freed et al., 2008) reflect mainly differences in buyer power in the U.S. Differences in public prices between countries with similar high per capita income levels are probably rooted in differences of willingness to pay, which are reflected in the cost-effectiveness criteria applied in most European countries, whereas the differences between the UNICEF/GAVI prices and the U.S. federal contract prices reflect mainly differences in the ability to pay.

Tiered pricing has a number of advantages. If firms were to charge only one price, this price would generally be what higher-income consumers can pay, which would make vaccines unaffordable to many lower-income consumers (Danzon et al., 2011). Tiered pricing increases equity by making vaccines available to most people regardless of their ability to pay. At the same time, it increases manufacturers' profits as long as the lowest price exceeds marginal cost. Profitability provides incentives for existing manufacturers to remain in the market and invest in R&D, resulting in better vaccines in the future (Lichtenberg, 2011). It may also attract new entrants, a socially desirable outcome although less favorable for incumbents.

The main danger of tiered pricing is that the low prices will trigger pressures to reduce prices to buyers who previously purchased at higher prices. Such reductions lower profitability, which may result in insufficient investments in manufacturing capacity and R&D, and lead firms to exit the market. The pressure to reduce prices is particularly high when the low prices are public and used as reference prices by high-price buyers. Price transparency, as recently implemented by UNICEF (McNeill Jr., 2011), can have the unintended effect to increase prices paid by the poor, deter entry in low-income markets, reduce competition, and lower investment (Kyle & Ridley, 2007).

Price referencing across countries is one reason why vaccine manufacturers tend to launch their products in high-income high-price countries first, even when the burden of disease may be highest in low-income countries. For example, the HPV vaccines were first launched in high income countries, in which cervical cancer mortality is low thanks to the widespread use of pap tests, while the major burden of cervical cancer arises in low income countries with little pap testing. Another reason for the launch sequencing is the difference in the burden of disease of HPV in the high-income countries, where most other infectious diseases are of lower concern, whereas other infectious diseases take precedence over HPV in low-income countries.

Vaccine manufacturers and most public buyers in high income countries use cost-effectiveness analysis to set and assess vaccine prices. Cost-effectiveness is a value-based

pricing method in which a vaccine's incremental cost per unit of health gain (often measured as quality-adjusted life-year or QALY) is compared with the buyer's maximum incremental cost per QALY gained. For example, the UK NITAG uses the guideline that the vaccine should result in an incremental cost of less than £30,000 per QALY gained (Hall, 2010). The Australian NITAG initially rejected Gardasil because it found that it was not cost-effective at the proposed price of \$450. When Gardasil was resubmitted at a significantly lower price, it was found to be cost-effective and publicly funded (Roughead et al., 2008).

In many high income countries, the cost-effectiveness methods used by public buyers to assess vaccines are the same as for other pharmaceuticals. But vaccines have specific features. They may provide herd immunity (unvaccinated or poorly vaccinated people may benefit), prevent illness in young children, which causes extra care and work loss, and prevent illness in distant years, which makes the cost-effectiveness results highly sensitive to different discount rates. They may also eradicate some infections, and prevent or control pandemics with potentially major macroeconomic impacts. These vaccine specificities are currently poorly captured in many economic evaluations, which may result in cost-effectiveness estimates that make vaccines unacceptable to buyers (Beutels et al., 2008).

4.6 Communication

The target audience, behavioral goals, communication goals, positioning objects, and communication channels for a vaccine depend on two market characteristics: (1) whether vaccination is mandatory or voluntary; and (2) whether physicians can choose between different brands (provider choice) or not.

When vaccination is mandatory and providers cannot choose, national or regional authorities mandate vaccination and choose one brand. They generally manage the entire immunization program including vaccine distribution, selection of vaccination settings and vaccinators, and immunization communication. Vaccine manufacturers' communication efforts are minimal in such situations, and targeted at public authorities. The behavioral goals are (a) to make vaccination mandatory, (b) win the contract in case there are competing suppliers, and (c) obtain a high price. The corresponding communication goals are to increase the need for vaccination, and to create brand preference and a high willingness to pay. This requires positioning the disease (Angelmar et al., 2007) in addition to positioning the brand and supplier. Personal selling via key account management is the key communication channel.

Situations where vaccination is voluntary and providers do not choose the brand are very similar to the previous case. Examples are the 2009 H1N1 campaigns in most countries,

and HPV vaccination in the UK and some other countries where governments chose one of the two competing HPV vaccines Gardasil and Cervarix. The main difference from the point of view of communication is that vaccine manufacturers may need to focus less on the need for vaccination and positioning the disease in the minds of authorities. For example, for H1N1 this was done mainly by WHO. Authorities, however, face a big challenge to convince consumers to vaccinate, especially if demand for vaccination is far lower than the amount of vaccines purchased. U.S. health authorities mounted a significant consumer communication effort using a broad range of media to use up their large stock of H1N1 vaccine doses (Anonymous, 2010).

Situations where vaccination is mandatory but physicians can choose between different brands of vaccine are more challenging for vaccine marketers and involve higher communication investments. Targeting physicians to achieve brand preference and brand recommendation to consumers typically requires face-to-face selling through medical representatives, plus other channels (medical journal advertising, congresses, continuing medical education, etc.).

Finally, the most challenging situation for vaccine marketers is where vaccination is voluntary, and physicians can choose brands. When vaccination is voluntary, this often means that there is a private market alongside the public market. Vaccine marketers must therefore direct sales efforts at public payers, private insurers, employers (for workplace immunization), health care professionals, and consumers. This situation and the communications strategies and tactics employed by vaccine marketers are very similar to those of therapeutics marketers, and marketing and sales expenditures also reach similar levels. For example, the communication strategies employed by Merck for its HPV vaccine Gardasil were comparable to those used for blockbuster therapeutics, earning Gardasil the “Brand of the Year” award (Herskovitz, 2007), the General Manager of Merck’s HPV Franchise the “Marketer of the Year” award (Applebaum, 2007), in addition to the accusation that the campaign “undercut the most cost-effective and appropriate use of new agents to the detriment of adolescent health” (Rothman & Rothman, 2009).

4.7 Distributing vaccines

Vaccinations are administered in a variety of settings including physician offices, pharmacies, supermarkets and other stores, the workplace, and schools. Easy access (minimal travel time and costs) to vaccination settings is important, which is not always the case, especially in low income countries. In a study in rural Pakistan, only 39% of enrolled children completed DTP3, and completion was higher among children who were living ≤ 10 minutes

away from an immunization center (Usman et al., 2010). In emergency situations such as a pandemic, public health authorities typically expand the number and types of vaccinations settings in order to increase the speed and rate of vaccination coverage.

Vaccines vary in stability and, thus, shelf life. Maintaining a cold chain that is robust, reliable, and routinely monitored for possible deviations is essential (Smith, Lipsitch & Pickering, 2011). A recent report points out that vaccines that do not need refrigeration and may be administered orally or intranasally “could dramatically transform the immunization landscape, removing or considerably lessening the logistical challenges, training requirements, and potential safety challenges related to vaccine management and administration” (Institute of Medicine, 2010, p. 210).

When its transportation and storage requirements exceed the capabilities of the supply chain participants, the commercial success of a vaccine is compromised. The need to remain frozen until used represented an important handicap for the success of MedImmune’s nasal spray flu vaccine FluMist, in addition to its high price. Many practices were lacking freezers, and many of those who did have freezers received FluMist in containers that were too big to fit into them (Appleby, 2004). FluMist’s sales increased significantly once it was reformulated for storage in a refrigerator rather than a freezer. The required supply chain capabilities concern not only technical but also staff competencies. One of the reasons why Gardasil had a much lower penetration among 19-26 year old women was that obstetricians/gynecologists, among the most important physician specialties for this age segment, had no prior vaccination experience and therefore lacked not only stocking capabilities but also the financial and logistics skills required for profitable vaccine dispensing.

5 Vaccine sales forecasting

A number of factors make it important to have accurate vaccine sales forecasts. First, vaccine manufacturing facilities require large investments and are typically uniquely dedicated (Berndt et al., 2009). Secondly, because of the long and complex manufacturing cycles (on average 15 to 20 months, with the notable exception of flu vaccines), the possibility to respond rapidly to higher demand is limited (Scherer, 2007). Thirdly, the limited shelf life of vaccines increases the risk that excess quantities cannot be sold and must be destroyed.

Accurate forecasts are particularly difficult for new vaccines against new disease targets, and for diseases the incidence of which fluctuates significantly such as seasonal flu and pandemics. A case in point is the 2009 H1N1 flu. The number of doses purchased by the U.S. government based on forecasts exceeded demand by about 70 million doses, representing 43%

of supply. The excess inventory, valued at about \$450 million, was subsequently destroyed (Bigongiari, 2010). Other countries had similar experiences.

Sales forecasting is easiest for vaccines which have a well established tradition of routine vaccination of an easily quantifiable and reachable target. This is the case for vaccinating birth cohorts with classical infant vaccines in developed countries.

Random demand shocks occur when competitors cannot supply due to quality problems. To protect the population against product shortages, the FDA requires vaccine manufacturers to hold an inventory corresponding to several months of sales.

Global vaccine sales forecasts are built “bottom-up” by combining country forecasts. Country vaccine forecasts use the same methods as the ones used generally for pharmaceuticals (Cook, 2006). New product forecasts multiply the eligible population by the expected vaccination rate and price. Such forecasts are generated by segments (e.g., by age groups, and public vs. private segment), and combined for country sales forecasts. Assumptions about the expected vaccination rates are based on analogies, market research, and judgment. Sales forecasts for in-market vaccines are generally based on statistical methods (trend extrapolation) combined with judgmental adjustments.

6 Trends in vaccines and vaccine marketing

Children have been the traditional consumer target group for the vaccine industry. Most vaccines still target children’s diseases, and publicly financed routine immunization programs in high income countries have provided the industry with a predictable revenue stream. But in recent years and in the future adolescents and adults will become increasingly important target groups for the industry (Silverman, 2009). Because these vaccines will be prescribed by a broader set of physician specialties than the current vaccine prescribers, vaccine marketers will need to develop new communication strategies and reallocate marketing resources.

The number of injections per person is increasing together with the number of vaccine-preventable diseases. This has triggered a move toward combination vaccines. To overcome needle-phobia, new methods of administering vaccines are being developed.

Faced with fiscal problems and escalating health care costs, public and private payers are looking for ways to allocate resources to the most cost-effective health interventions. Providing robust evidence of cost-effectiveness will be a future key factor for winning against other vaccines and other types of health interventions.

The current domination of the global vaccine market by the big five will be challenged by manufacturers from emerging markets. The Chinese government has woken up to the

importance of the vaccine industry and has taken a number of measures to strengthen it (ResearchInChina, 2011). Manufacturers from India – and soon from China - challenge the big five in low income countries and in internationally-funded tenders, and will be increasingly present in middle income countries over the coming decade. Regulatory changes regarding biosimilars may facilitate the entry of biosimilars and shorten the life cycle of branded original vaccines.

The development of therapeutic vaccines targeting disease-specific proteins in such fields as oncology and immune diseases could herald a new era for the vaccine market. As discussed at the beginning of the chapter, therapeutic vaccines are similar to other therapeutic biologics in that they focus on solving consumers' current health problems, generate benefits to only to individuals and not communities, and will command prices far exceeding those of preventive vaccines.

7 Promising research questions for marketing scholars

We first discuss three priority questions for vaccine marketers and public health policy makers, followed by some other promising research questions, and then discuss the availability of data on vaccine markets.

7.1 Maintaining high vaccination rates despite the quasi-absence of targeted diseases

When consumers' vaccination behavior is prevalence-elastic, voluntary vaccination programs can be victims of their own success. How can vaccine marketers maintain consumers' motivation to vaccinate despite the quasi-absence of the targeted disease? Conceivably, the same issue could pose itself for physicians.

Raising the perceived threat of the disease is one strategy. This could be done by communicating the consequences of outbreaks in other countries or in parts of a country. MacDonald et al. (in press) cite polio outbreaks in Europe and pertussis outbreaks with infants dying in California as communication opportunities, as well as the possibility to highlight the link between outbreaks and a drop in the vaccination rate. Downward counterfactual messaging (Epstude & Roese, 2008; e.g., “without vaccination, X children would have died”) could also be employed.

The quasi-absence of a targeted disease reduces the perceived disease risk and, thereby, also the direct benefits of vaccination. Raising the total vaccination benefits through emphasizing the indirect social and altruistic benefits of vaccination is another possible strategy

(Hershey et al., 1994; Skea et al., 2008; Reyna, in press; Caplan, 2011). As Weinreb (2011) argues, “getting vaccinated ... is just another important social responsibility”. Altruism has been found to be an important motivator for participation in HIV vaccine trials, in addition to personal benefits (Balfour et al., 2010; Dhalla & Poole, 2011).

Communicating that vaccination is a norm represents a third strategy. Hershey et al. (1994) recommend that communications should stress high vaccination rates, thus using descriptive norms (Smith-McAllen & Fishbein, 2008) or social proof (Cialdini, 2009).

Evidence on the relative effectiveness of the different possible strategies is lacking.

7.2 How to reduce the percentage of people who refuse or delay vaccination

Increasing numbers of parents refuse or delay vaccination for their children, mainly because safety concerns associated with vaccines loom larger than their benefits (Omer et al., 2009; Smith, Humiston et al., 2011; Salmon et al., 2005). Moreover, the many parents who let their children be vaccinated despite harboring significant safety concerns might join the camp of refusers and delayers unless their concerns are effectively addressed (Freed et al., 2010; Kennedy et al., 2011a, b).

Reyna (2011) emphasizes the importance of understanding how individuals represent the gist or meaning of risk messages and recommends two strategies for making the perceived risk of non-vaccination higher than that of vaccination. The “categorical (nominal)” strategy makes not vaccinating the risky choice (“gambling on avoiding the disease”) by conveying that the risks of vaccination are “nil”. The “ordinal” strategy compares the larger risks of disease to the lower risks of the vaccine. She also suggests raising the risks of non-vaccination by adding indirect risks to the community to the personal risks, a loss-framing of the social consequences (e.g., “by not getting vaccinated you are a socially irresponsible person”).⁴⁰ However, because many consumers lack an understanding of herd immunity (Downs et al., 2008), increasing their background knowledge may be necessary.

Koehler and Gershoff’s (2003) findings suggest that perceiving vaccination as the less risky option may not be sufficient to trigger vaccination, because consumers tend to choose options that provide less overall protection in order to eliminate a very small probability of harm due to safety product betrayal. Reasoning that safety product betrayal causes strong negative emotions, which favor emotional (system 1) appraisals, they propose that dampening the emotional response to potential betrayals promotes a more cognitive (system 2) appraisal, which would result in a preference for the lower-risk option (Gershoff & Koehler, 2011). They test five tactics in a non-vaccine context which find this to be the case.

Anticipated regret has been identified as a strong predictor of vaccination behavior (Brewer et al., 2010; Chapman & Coups, 2006; Weinstein et al., 2007) but not tested as a potential communication strategy for vaccines.

Because health care professionals are the most important information source for vaccination decisions (Kennedy et al., 2011a), they are the key communication channel for delivering messages that change the benefit-risk balance, manage consumers' pre-decisional emotions, and persuade them to vaccinate. But the effective use of this channel faces important obstacles: (1) Insufficient evidence regarding the effectiveness of the different possible strategies and messages, for different types of consumers. Theory- and research-based recommendations such as the ones by Reyna, Gershoff and Koehler need to be tested in a vaccination context. There is a wealth of other recommendations about how to communicate with vaccine-refusing or -hesitant consumers (e.g., Healy & Pickering, 2011), but few attempts at empirical validation (Gust et al., 2008, 2009). (2) Assuming effective messages for different consumer segments were identified, health care professionals would have to be trained to rapidly identify to which segment an individual consumer belongs, and deliver the appropriate message, analogous to what pharmaceutical sales representatives do during a sales call. (3) Not all health care professionals are strongly convinced of the safety and benefits of vaccines. A study of primary care providers found that those providing care for unvaccinated children were less likely to have confidence in vaccine safety and perceive their benefits for individuals and communities than those providing care for appropriately vaccinated children (Salmon et al., 2008). Communication strategies and messages to change the beliefs and attitudes of these health care professionals therefore also need to be developed.

7.3 Combating anti-vaccination information

Anti-vaccination information can be found in popular television programs such as the Oprah show (Parikh, 2008), on anti-vaccination websites (Bean, 2011; Kata, 2010, in press), online discussion forums (Nicholson & Leask, in press), in viral videos on YouTube (Briones et al., in press), and other media. Typical claims of anti-vaccination websites are that vaccines are not safe and effective and that vaccination restricts civil liberties. The most recent study (Bean, 2011) identified two emerging trends: a rise in conspiracy theories following the 2009 H1N1 epidemic threat which is claimed to have been "manufactured" by vaccine suppliers and allied players, and the increased use of anti-vaccine testimonials by "experts" (e.g., unidentified doctors). Anti-vaccination information increases the perceived risk and lowers vaccination

intentions (Betsch et al., 2010), particularly when the information consists of highly emotional narratives (testimonials, anecdotes) (Betsch et al., 2011).

The traditional strategy of fighting anti-vaccination information with education and evidence-based communication is considered to have been ineffective (Parikh, 2008; Reyna, 2011; MacDonald et al., 2011; Caplan, 2011). Alternative proposed strategies include emphasizing “simple bottom-line meaning” instead of facts and details (Reyna, 2011), stressing the obligation to act as a moral member of a community (Caplan, 2011), including more emotionally compelling content (Bean, 2011), for example, by having a parent tell a story of how their child died from a disease which could have been prevented by vaccination (Parikh, 2008), enhancing the knowledge of the vaccine safety system (MacDonald et al., 2011), and increasing the engagement of health professionals and other vaccination advocates in online discussion forums (Nicholson & Leask, 2011).

Marketing scholars can contribute to the development of effective strategies for combating anti-vaccination information by extending research on anti-rumor and brand-scandal strategies (e.g., Tybout et al., 1981; Roehm & Tybout, 2006), message framing strategies that mobilize social motivations (e.g., Zhao & Pechmann, 2007), and consumer persuasion knowledge models (Campbell & Kirmani, 2008) which might help fight conspiracy theories, among others.

7.4 Other consumer behavior research questions

Consumer belief-behavior causality. Most studies about vaccination perceptions and behavior are cross-sectional. Because of this, the direction of causality – do the beliefs cause vaccination behavior, or does causality flow in the other direction? – is not clear (Weinstein, 2007). Longitudinal studies (e.g., Ibuka et al., 2010) could clarify causality. Funk et al. (2010) also stress the need for empirical parameterization of the many mathematical models of infectious disease-vaccination dynamics, and discuss potential technologies for collecting longitudinal data.

Vaccine fatigue. A number of new vaccines for new markets are expected to be launched over the coming years. According to Humiston et al. (2009) physicians feel that, faced with an increasing number of recommended vaccines, parents are exhibiting “vaccine fatigue”. Kennedy et al. (2011a) found converging results.⁴¹ Unless vaccine marketers find ways to overcome this vaccine fatigue, the success of future new vaccine launches will be compromised.

7.5 Competitive strategy research questions

Pricing. The recent publication by UNICEF of prices for individual vaccines (McNeill Jr., 2011) provides a natural experiment for testing hypotheses (Kyle & Ridley, 2007) about the impact of price transparency on companies' pricing strategies and other decisions. The contract prices for vaccines published together with the manufacturers' list prices on the CDC website show great variation in the contract price discounts. What explains the differences in discounts?

Market share dynamics. Consumers and sales in a product class can be divided into "static" and "dynamic" components. The dynamic component consists of product class starters, brand switchers, and existing consumers which add a brand, while the static component comprises consumers who continue on their current treatment (Harold & Odqvist, 2011). The greater the dynamic share in a class, the higher the potential for market share changes. Because most preventive vaccines are administered only once or very infrequently over a life time, virtually all sales are to product class starters (new consumers). Market shares therefore are potentially highly volatile. Analogous to studies in other markets (Sutton, 2007; Srinivasan & Bass, 2000; Dekimpe & Hanssens, 1995), marketing scholars could investigate market share dynamics and explore determinants of market share volatility.

Budget competition. The fiscal and economic crisis in many countries increases the need for governments and other payers to make trade-offs between new and older vaccines, and between vaccines, therapeutics and other health interventions. Pure vaccine players can position vaccines against therapeutics, but players with both types of pharmaceuticals must find ways to ensure that payers are willing to increase spending for both.

7.6 Vaccine market data

Searching the "Research and Markets" database with the word "vaccine" results in over 3,000 results.⁴² Publishers of reports generally used by vaccine marketers for global market evaluation include Datamonitor, Frost & Sullivan, GBI research, and Kalorama.

IMS Health sales data, which are widely used by therapeutics marketers and marketing scholars unfortunately do not provide reliable results for most vaccines. Sales through wholesale and retail channels, the basis of IMS Health sales data, capture only part of vaccine sales. A significant other part is shipped directly from manufacturers to prescribers, or to public purchasers who distribute them to prescribers (Berndt et al., 2009). The share of total vaccines sales captured by IMS Health data is estimated at 70% for the U.S., between 50% and 90% for Western European countries, and less than 20% for China.

Because of the lack of reliable syndicated sales data, companies like Sanofi-Pasteur have developed their own complex data collection system which combines data from multiple sources.

8 Conclusion

In 2010, the Bill & Melinda Gates Foundation declared this decade « The Decade of Vaccines ». Not long ago perceived as an unattractive segment of the pharmaceutical industry, most of the leading firms have revised their opinion and increased their investments in vaccines. In preparing this chapter, we have found very few articles dealing with vaccines in the marketing literature. We hope that marketing academics will follow the lead of the pharmaceutical industry and devote more attention to vaccines during this decade.

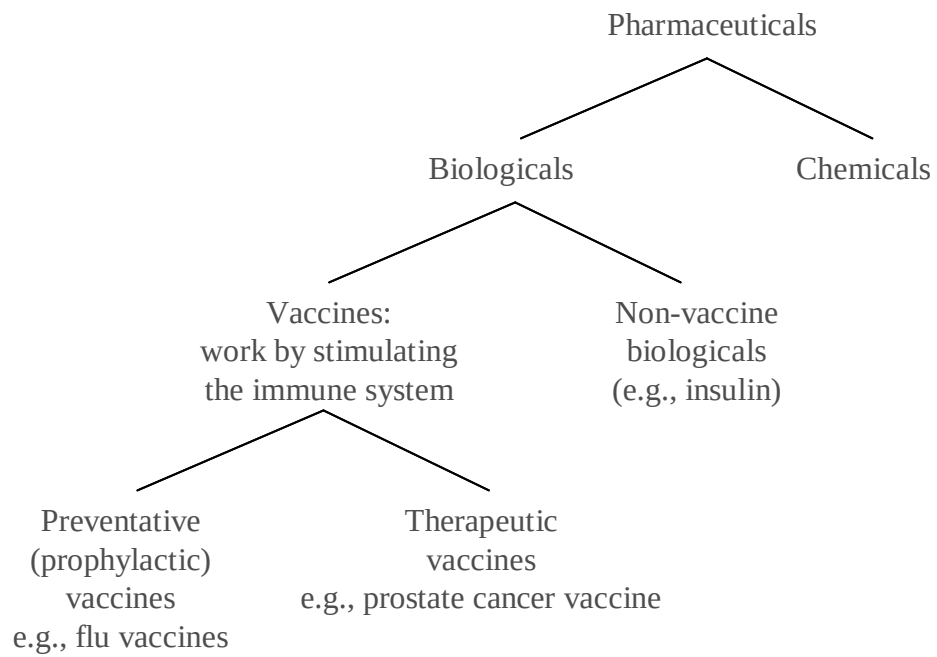
Figure 1Types of pharmaceutical products

Table 1Leading Global Vaccine and Pharmaceutical Corporations, 2010

Leading Global Vaccine Corporations, 2010					Leading Global Pharmaceutical Corporations, 2010				
		Global Sales*	Market	Cumulative Market			Global Sales***	Market	Cumulative Market
Rank		(\$m)	Share	Share	Rank		(\$m)	Share	Share
1	GlaxoSmithKline	6,712	23%	23%	1	Pfizer	55,602	7.0%	7%
2	Sanofi**	5,663	20%	43%	2	Novartis	46,806	5.9%	13%
3	Merck & Co**	4,117	14%	57%	3	Merck & Co	38,468	4.9%	18%
4	Pfizer	3,667	13%	70%	4	Sanofi	35,875	4.5%	22%
5	Novartis	2,929	10%	80%	5	AstraZeneca	35,535	4.5%	27%
6	Others	5,743	20%	20%	6	GlaxoSmithKline	33,664	4.3%	
Global Market		28,833		100%	Global Market		791,449		100.0%

* Source: sales of top 5 companies based on GSK broker presentation; sales for "others" assume the top 5 firms account for 80% of the global vaccine market (Kresse & Shah, 2010).

** The sales of Sanofi Pasteur MSD are allocated 50/50 to Sanofi and Merck & Co

*** Source: IMS Health; sales for audited markets only

Table 2Revenue structure: Vaccines and pharmaceuticals

	GlaxoSmithKline Vaccines ¹	Sanofi Vaccines (Sanofi Pasteur) ²	Pharmaceuticals ³
Cost of goods sold	38%	38%	21%
R & D	17%	14%	18%
Marketing, Sales & Administrative	17%	17%	31%
Operating profit	29%	32%	30%

¹ 1st quarter of 2011 (first time vaccine P&L was separately reported).

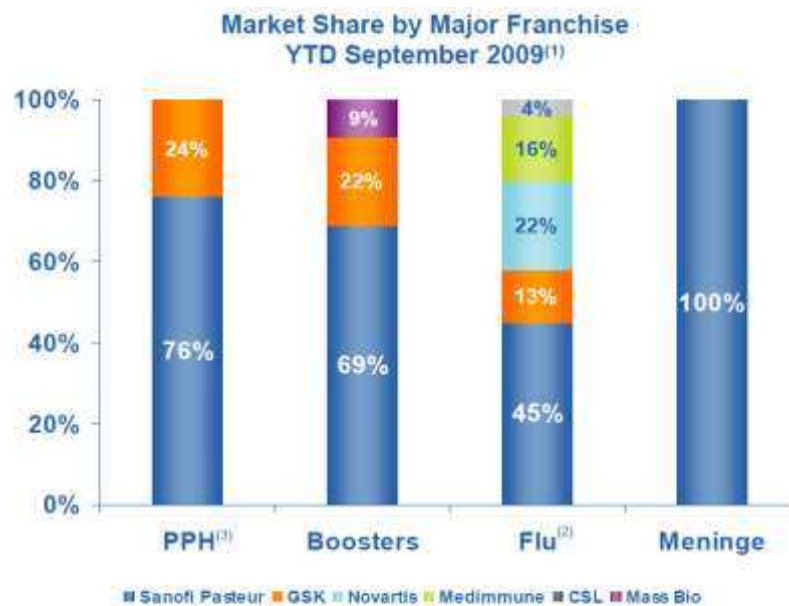
² average of 2008-2010. Percentage of net sales

³ Average of 32 originator companies. Source: European Commission, 2009

Table 3Competitor shares by selected regions and countries

	Western Europe	Latin America	China	India	Russia
Sanofi Pasteur		29%	10%	36%	20%
Sanofi Pasteur MSD	36%				
GlaxoSmithKline	30%	23%	10%	12%	8%
Merck & Co		6%	Other	NA	2%
Pfizer	16%	27%	multinational	NA	NA
Novartis	7%	2%	companies: 3%	10%	2%
Sub--total	89%	87%	23%	58%	32%
Others	11%	13%	77%	42%	68%

Source: Sanofi Aventis, Vaccines IR Seminar, December 17th, 2009

Figure 2Competitor share in selected franchises, North America

(1) Third Quarter 2009 GSK Quarterly Earnings Statements and Sanofi Pasteur internal sales data

(2) Internal Forecasts based on published CDC and manufacturer statements

(3) PPH – polio, pertussis, Hib

Source: Sanofi Aventis, Vaccines IR Seminar, December 17th, 2009

Table 4

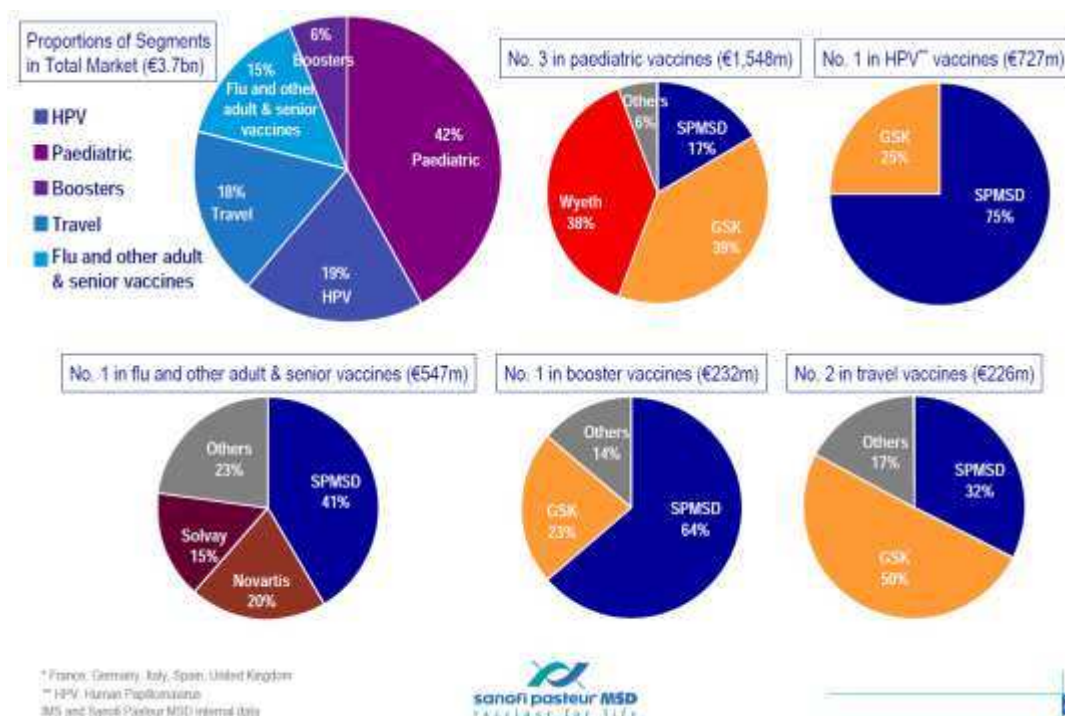
Number of vaccine manufacturers of ACIP-recommended vaccines posted on
CDC vaccine price list, November 5, 2008

Number of manufacturers per vaccine/age class	Nr of vaccine/age classes	% of all vaccine/age classes
1	17	57%
2	10	33%
3	1	3%
4	1	3%
5	1	3%
Total number of vaccine/age classes on CDC List	30	100%

Source: based on Table 3-1 in Berndt et al. (2009).

Figure 3

Competitor share in selected franchises, Western Europe

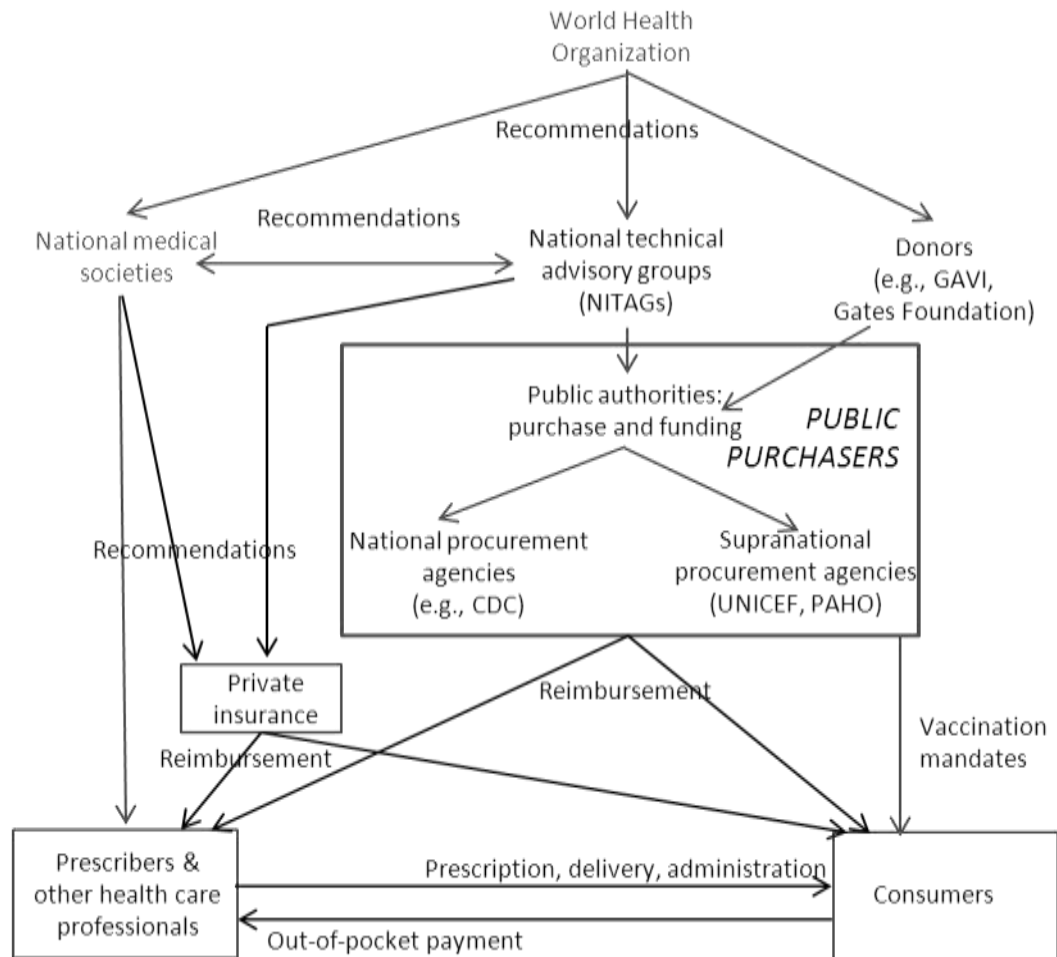


Source: Sanofi Aventis, Vaccines IR Seminar, December 17th, 2009

Table 5
Customer roles and examples of role holders in the vaccine market

Customer role	Role definition	Examples of persons and organizations carrying out the role
Consumer	person who is vaccinated	children, adolescents, adults
Buyer	persons / organizations selecting the vaccine which is used	consumers prescribers National Immunization Technical Advisory Groups (NITAGs), e.g., Advisory Committee on Immunization Practices (ACIP) in the U.S. governments supra-national organizations, e.g., Strategic Advisory Group of Experts (SAGE) at the World Health Organization (WHO); UNICEF; Pan American Health Organization (PAHO)
Payer	persons / organizations financing the purchase	consumers private insurances federal and regional (state) governments in the vaccinating country NGOs, e.g., GAVI, and other international donors

Figure 5
Customers in the vaccine market



¹ Some vaccines can be used both for prevention and treatment. For example, rabies vaccines can also be administered after an individual has been exposed to the virus (e.g., following a bite by a rabid dog).

² Provenge's sales have proven disappointing so far. <http://blogs.wsj.com/health/2011/08/04/dendreon-shares-plummet-as-company-withdraws-provenge-sales-forecast/>

³ Their slower onset of action compared with other therapeutic biologics represents a specific challenge for therapeutic vaccines.

⁴ State-owned vaccine manufacturers include the China National Biotech group (CNBG), the largest vaccine manufacturer in China, the Central Research Institute in India, Butantan and Fiocruz in Brazil, and PT Biofarma in Indonesia..

⁵ On March 1, 2011, WHO announced that the national regulatory authority of China met WHO indicators for a functional vaccine regulatory system, which meant that Chinese-made vaccines were henceforth eligible to apply for WHO pre-qualification.

⁶ The 4% share refers to volume. The value share of non-Japanese manufacturers is estimated at 20% (private communication, industry executive from Japan).

⁷ Depending on the state, children must be vaccinated against some or all of the following diseases: mumps, measles, rubella, diphtheria, pertussis, tetanus, and polio.

⁸ For example, state legislation in California requires that all students < 19 years in state universities and the UC system provide proof of Hepatitis B vaccination or a waiver. <http://www.immunize.org/laws/hepbcollege.asp>, accessed June 13, 2011

⁹ For example, New Hampshire requires that all hospital employees and inmates receive flu vaccination.

¹⁰ <http://www.vaccinesafety.edu/cc-exem.htm>, accessed June 13, 2011

¹¹ http://ecdc.europa.eu/en/publications/Publications/2011_June_measles_monthly.pdf, accessed August 31.

¹² A comprehensive review by the IOM (Institute of Medicine) (2011) concluded that the evidence favors rejection of a causal relationship between MMR vaccine and autism, and that there is inadequate evidence to accept or reject a causal relationship between hepatitis B vaccine and multiple sclerosis.

¹³ Some ITAGs have broader mandates to work in other areas of communicable disease control (Gessner et al., 2010).

¹⁴ For example, the NITAG in the UK is the Joint Committee on Vaccination and Immunisation (JCVI) (Hall, 2010). Australia has the Australian Technical Advisory Group on Immunisation (ATAGI) (Nolan, 2010), China the Experts Advisory Committee on Immunization Program (EACIP) (Zheng et al., 2010), and South Africa the National Advisory Group on Immunization (NAGI) (Schoub et al., 2010). More information on NITAGs can be found in *Vaccine* 28S (2010).

¹⁵ The SIVAC Initiative (Senouci et al., 2010) and PAHO's ProVac Initiative (Jauregi et al., 2011), both funded by the Bill & Melinda Gates Foundation, have as their main mission to help countries establish or strengthen their NITAG's capacity to make informed, evidence-based decisions on the introduction of new vaccines.

¹⁶ As of 1 January 2010, ACIP liaison representatives include include representatives from the American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP; two representatives), American College of Obstetricians & Gynecologists (ACOG), American College of Physicians (ACP), and American Medical Association (AMA), among others (Smith, 2010).

¹⁷ The list includes 4 agencies in the Americas (US, Canada, Brazil, Cuba), 11 agencies in Europe, 5 in Asia (China, India, Indonesia, Japan, Korea), Senegal, and Australia. http://www.who.int/immunization_standards/national_regulatory_authorities%20/offices/en/index.html/, accessed August 15, 2011. The Chinese State Food and Drug Administration (SFDA) achieved joined the list in March 2011. http://www.who.int/immunization_standards/vaccine_regulation/nra_china_functional/en/, accessed August 15, 2011.

¹⁸ An example of a recent delisting announcement can be found at the following address: http://www.who.int/immunization_standards/vaccine_quality/DTP_mono_hepb_aug2011/en/index.html, accessed August 23, 2011.

¹⁹ To make a UK NITAG recommendation binding, the recommendation must be based on a question specifically referred by the Secretary of State, be based on an assessment which demonstrates cost-effectiveness, and not relate to travel or occupational health (Hall, 2010).

²⁰ CDC provides funds to states and other jurisdictions under the VFC program, which finances all ACIP-recommended childhood vaccines, and Section 317 funds, a program for which there are no eligibility requirements. The 317 funds must be appropriated each year by Congress.

²¹ States purchase directly from a manufacturer when there is no federal contract for a specific vaccine, and when they are not allowed to rely on the federal contract for a vaccine, because they are using non-federal funds, particularly funds from insurance companies (Benatar et al., 2010). Despite their smaller purchase volume, some states have reported instances in which they were able to negotiate a price below the federal contract price (Freed & Cowan, 2002).

²² The Gulf Cooperation Council (GCC), which procures vaccines for the UAE, Bahrain, Saudi Arabia, Oman, Qatar, and Kuwait, is another supranational vaccine procurement agency. See DeRoeck et al. (2006) for a review of the GCC).

²³ Excluding China, India and Indonesia, 92% of the 2007 birth cohort in low income, and 47% of the birth cohort in lower middle income countries were covered by UNICEF procurement. The percentage of UNICEF procurement in high income OECD countries was 0%, 2% in high income non-OECD countries, and 1% in lower middle income countries (Rosenbom, 2010).

²⁴ http://www.unicef.org/supply/index_vaccines.html, accessed August 22, 2011

²⁵ UNICEF procures for governments, NGOs, UN agencies, international financial institutions, philanthropic organizations, and universities, but not for profit-making entities and individuals.

²⁶ http://www.unicef.org/supply/index_57476.html

²⁷ As of August 2001, the 35 member states include Argentina, Brazil, Canada, Mexico, and the US, among others.

²⁸ http://new.paho.org/hq/index.php?option=com_content&task=view&id=1864&Itemid=2234&lang=en

²⁹ The number of potentially supported vaccines expanded from the initial three (vaccines against Hib, Hepatitis B and Yellow Fever) to currently six (pneumococcal, rotavirus and meningococcal A conjugate vaccines).

³⁰ For GAVI-eligible countries in Latin America, PAHO is GAVI's primary procurement partner (Anonymous, 2011).

³¹ http://www.unicef.org/supply/index_gavi.html, accessed August 23, 2011

³² <http://www.gavialliance.org/library/news/press-releases/2011/donors-commit-vaccine-funding-to-achieve-historic-milestone-in-global-health/>, accessed August 23, 2011. Donors (governments, foundations, private individuals and companies) support GAVI through direct funding, long-term pledges to the International Finance Facility for Immunisation (IFFIm), an innovative financing mechanism which converts the commitments into immediately available cash resources by issuing bonds on the capital markets; and long-term pledges to the Advance Market Commitment (AMC) for pneumococcal disease (Kremer, 2001; Snyder et al., 2011).

³³ There is also an unofficial route in which pharmacists dispense a vaccine to regular clients, who subsequently return with the prescription obtained during the vaccine administration visit.

³⁴ Spreading purchases over several brands also reduces the profit margin because of higher purchase prices due to a lower purchase volume per brand.

³⁵ All new health plans, and health plans that lose their grandfathered status, must provide all ACIP-recommended vaccines delivered by an in-network provider at no cost sharing.

³⁶ <http://www.cdc.gov/vaccines/vpd-vac/default.htm#newvacc>, accessed August 28, 2011

³⁷ The H1N1 pandemic raised fears that it might spread to the flocks that produce the eggs required for flu vaccine production and thereby strangle vaccine supply. This stimulated the development of new process technologies such as cell-based production systems which are expected to increase the speed and volume of flu vaccine supply (Extance, 2011).

³⁸ <https://www.medicalcountermeasures.gov/FederalInitiatives.aspx>

³⁸ For example, in February 2011 Novavax received a contract from BARDA for up to \$180 million for the development of a recombinant flu vaccine. And the U.S. government invested over a billion dollars to help vaccine companies make the transition from traditional egg-base to cell-based production systems (Extance, 2011).

⁴⁰ In Skea et al.'s (2008) study, some parents were quite critical of other parents who did not vaccinate healthy children.

⁴¹ 27.8% of parents agreed that "children get too many vaccines during the first 2 years of life", and 21.9% of them strongly/somewhat agreed with the statement "I am concerned that my child's immune system could be weakened by too many vaccines".

⁴² <http://www.researchandmarkets.com/search.asp?q=vaccines>

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Europe Campus
Boulevard de Constance
77305 Fontainebleau Cedex, France
Tel: +33 (0)1 60 72 40 00
Fax: +33 (0)1 60 74 55 00/01

Asia Campus
1 Ayer Rajah Avenue, Singapore 138676
Tel: +65 67 99 53 88
Fax: +65 67 99 53 99

Abu Dhabi Campus
Muroor Road - Street No 4
P.O. Box 48049
Abu Dhabi, United Arab Emirates
Tel: +971 2 651 5200
Fax: +971 2 443 9461

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